Comparative Effectiveness Review
Number 173

Diabetes Medications for Adults With Type 2 Diabetes: An Update

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Effective Health Care Program

Comparative Effectiveness Review

Number 173

Diabetes Medications for Adults With Type 2 Diabetes: An Update

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Addendum and Errata

Introduction

During report dissemination in a peer-reviewed journal, Annals of Internal Medicine requested an update of our search and evidence.

Methods

Search Strategy

We updated the MEDLINE search to identify randomized controlled trials indexed through December 31, 2015.

Evidence Grading

We updated the evidence from the final Agency for Healthcare Research and Quality report with results from newly identified randomized trials if these results increased the strength of evidence from low or moderate to moderate or high.

Results

From the updated MEDLINE search, we identified eight new studies (published in nine articles)[1-9] which met our inclusion criteria, plus six additional publications that were either extensions or additional analyses of included studies.[10-15] Of these, four studies contributed results which increased the strength of evidence to moderate or high strength; the results of these studies were incorporated in the publication (Appendix Figure 1).[16] The updated strength of evidence is shown in Table 1. We report four new findings: (1) sulfonylureas had greater reductions in hemoglobin A1c than dipeptidyl peptidase-4 (DPP-4) inhibitors; (2) sulfonylureas had less beneficial effects on weight than DPP-4 inhibitors; (3) metformin plus glucagon-like peptide-1 receptor agonists had greater weight reductions than metformin plus premixed insulins; and (4) metformin plus thiazolidinediones had less diarrhea than metformin alone (Figures 1 and 4; Appendix Table 6 in the Annals of Internal Medicine manuscript[16]).

Conclusions

These four new findings strengthen the overall conclusions from the main report.[17]

Table 1. Strength of evidence domains for the comparisons and outcomes that changed with the updated search

Comparison	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary
SU vs. DPP-4 inhibitors	HbA1c	4 (1659)	Medium	Consistent	Direct	Precise	Undetected	Moderate	SU favored; pooled mean between-group difference, -0.2% (95% CI, -0.3 to -0.1%)
SU vs. DPP-4 inhibitors	Weight	4 (1659)	Low	Consistent	Direct	Precise	Undetected	Moderate	DPP-4 inhibitors favored; range in between-group differences of 0.7 to 1.8 kg
Metformin + GLP-1 receptor agonists vs. metformin + premixed insulin	Weight	2 (426)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 receptor agonists favored; range in between-group differences 1.9 to 5.1 kg
Metformin vs. metformin + TZD	GI side effects	11 (4,271) 6 studies on diarrhea; 1-2 studies for other GI-related outcomes	Medium	Consistent	Direct	Imprecise	Undetected	Moderate for diarrhea; Low for other GI-related outcomes	Metformin + TZD favored for diarrhea; Neither favored for other GI-related outcomes

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GI = gastrointestinal; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; GI = gastrointestinal; kg = kilograms; SU = sulfonylurea; TZD = thiazolidinedione

References

1. Yang W, Han P, Min KW, et al. Efficacy and safety of dapagliflozin in Asian patients with type 2 diabetes after metformin failure: A randomized controlled trial. J Diabetes. 2015 Nov 20.
2. Lu Y, Rodriguez LA, Malgerud L, et al. New-onset type 2 diabetes, elevated HbA1c, anti-diabetic medications, and risk of pancreatic cancer. Br J Cancer. 2015 Dec 1;113(11):1607-14.
3. Tanaka K, Saisho Y, Manesso E, et al. Effects of Liraglutide Monotherapy on Beta Cell Function and Pancreatic Enzymes Compared with Metformin in Japanese Overweight/Obese Patients with Type 2 Diabetes Mellitus: A Subpopulation Analysis of the KIND-LM Randomized Trial. Clin Drug Investig. 2015 Oct;35(10):675-84.
4. Ma Z, Chen R, Liu Y, et al. Effect of liraglutide vs. NPH in combination with metformin on blood glucose fluctuations assessed using continuous glucose monitoring in patients with newly diagnosed type 2 diabetes. Int J Clin Pharmacol Ther. 2015 Nov;53(11):933-9.
5. Hartley P, Shentu Y, Betz-Schiff P, et al. Efficacy and Tolerability of Sitagliptin Compared with Glimepiride in Elderly Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control: A Randomized, Double-Blind, Non-Inferiority Trial. Drugs Aging. 2015 Jun;32(6):469-76.
6. Cai XL, Chen YL, Zhao JJ, et al. Efficacy and safety of avandamet or uptitrated metformin treatment in patients with type 2 diabetes inadequately controlled with metformin alone: a multicenter, randomized, controlled trial. Chin Med J (Engl). 2015 May 20;128(10):1279-87.
7. Xiao CC, Ren A, Yang J, et al. Effects of pioglitazone and glipizide on platelet function in patients with type 2 diabetes. Eur Rev Med Pharmacol Sci. 2015;19(6):963-70.
8. Ross S, Thamer C, Cescutti J, et al. Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: a 16-week, randomized, placebo-controlled trial. Diabetes Obes Metab. 2015 Jul;17(7):699-702.
9. Tanaka K, Saisho Y, Kawai T, et al. Efficacy and safety of liraglutide monotherapy compared with metformin in Japanese overweight/obese patients with type 2 diabetes. Endocr J. 2015;62(5):399-409.
10. Roden M, Merker L, Christiansen AV, et al. Safety, tolerability and effects on cardiometabolic risk factors of empagliflozin monotherapy in drug-naive patients with type 2 diabetes: a double-blind extension of a Phase III randomized controlled trial. Cardiovasc Diabetol. 2015;14(1):154.
11. Chirila C, Zheng Q, Davenport E, et al. Treatment satisfaction in type 2 diabetes patients taking empagliflozin compared with patients taking glimepiride. Qual Life Res. 2015 Sep 30.
12. Li D, Xu X, Zhang Y, et al. Liraglutide treatment causes upregulation of adiponectin and downregulation of resistin in Chinese type 2 diabetes. Diabetes Res Clin Pract. 2015 Nov;110(2):224-8.
13. Simo R, Guerci B, Schernthaner G, et al. Long-term changes in cardiovascular risk markers during administration of exenatide twice daily or glimepiride: results from the European exenatide study. Cardiovasc Diabetol. 2015;14:116.

14. Li R, Xu W, Luo S, et al. Effect of exenatide, insulin and pioglitazone on bone metabolism in patients with newly diagnosed type 2 diabetes. Acta Diabetol. 2015 Dec;52(6):1083-91.
15. Weinstock RS, Guerci B, Umpierrez et al. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. Diabetes Obes Metab. 2015 Sep;17(9):849-58.
16. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: Systematic Review and Meta-Analysis. Ann Intern Med. 2016;In press.
17. Bolen S, Tseng E, Hutfless S, et al. Diabetes Medications for Adults with Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 173. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) Rockville, MD: Agency for Healthcare Research and Quality; April 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm

Errata

Upon closer review, we found that the primary outcome for Hong 2013 was indeed a composite cardiovascular outcome, which was not what we had stated and that the followup time was 5.0 years rather than 3.0 years. We also note that in the Executive Summary we stated that metformin and GLP-1 receptor agonists were similar for diarrhea, but this was of low and not moderate or high strength and therefore should have not appeared in that section.

This report is based on research conducted by the Johns Hopkins University Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2012-00007-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Diabetes Medications for Adults With Type 2 Diabetes: An Update

Structured Abstract

Objectives. To evaluate the comparative effectiveness and safety of monotherapy and metformin-based combination therapy for type 2 diabetes.

Data sources. We searched MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) for English-language articles using the search developed for the prior review (2011), with date restrictions of April 2009 through April 2015. We searched Drugs@FDA and ClinicalTrials.gov for unpublished data.

Review methods. Two reviewers independently reviewed titles, abstracts, and full-text articles to identify studies that assessed intermediate and clinical outcomes or safety for monotherapy (metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 [DPP-4] inhibitors, glucagon-like peptide-1 [GLP-1] agonists, and sodium glucose cotransporter-2 [SGLT-2] inhibitors) or metformin-based combination therapy (metformin plus one of these monotherapy drugs or insulin) comparisons. Two reviewers extracted data from included articles sequentially using standardized protocols; risk of bias was assessed independently. Two reviewers graded the strength of the evidence sequentially using a protocol adapted from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.

Results. We included 216 studies and found moderate- or high-strength evidence for the following. Hemoglobin A1c (HbA1c) reduction was similar across all monotherapy comparisons and across metformin-based combination comparisons except DPP-4 inhibitors, which yielded smaller reductions than metformin. Metformin, DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors reduced or maintained body weight, while sulfonylureas, thiazolidinediones, and insulin increased weight; between-group differences ranged from 1 to 5 kilograms. SGLT-2 inhibitors and GLP-1 agonists plus metformin reduced systolic blood pressure by 3 to 5 mmHg compared with metformin. Cardiovascular mortality in studies over 2 years in duration was 50 to 70 percent higher for sulfonylureas than metformin (risk difference, 0.1% to 2.9% in randomized controlled trials). Sulfonylurea-based therapy increased the risk of total and severe hypoglycemia versus most comparisons. Gastrointestinal adverse events were higher with metformin than other drugs except GLP-1 agonists, which increased nausea/vomiting 1.5 times compared with metformin. SGLT-2 inhibitors increased the risk of genital mycotic infections over other drugs. The evidence did not support substantive conclusions for microvascular outcomes, congestive heart failure, cancer, pancreatitis, or other safety outcomes.

Conclusions. Evidence from this updated systematic review supports metformin as firstline therapy, given its beneficial effects on HbA1c, weight, and cardiovascular mortality (relative to sulfonylureas) and its relative safety profile. In addition, evidence on comparative outcomes associated with different medication classes can be used to facilitate personalized treatment choices by patients and clinicians, guideline development, and decisionmaking by payers and regulators.

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Executive Summary

Condition and Therapeutic Strategies

Type 2 diabetes affects more than 9.3 percent of the U.S. population, or 29.1 million people.[1] Diabetes and its complications are a substantial public health burden, as they contribute significantly to mortality, morbidity, and health care costs.[1] Complications of longstanding diabetes include the microvascular complications of retinopathy and blindness, neuropathy, nephropathy, and end-stage kidney disease. Diabetes also contributes importantly to macrovascular complications, including coronary artery disease, peripheral arterial disease, and carotid artery disease, and increases the risk of cardiovascular-related death nearly twofold.[2] Lifestyle modification and pharmacologic therapy are the cornerstones of the management of hyperglycemia for type 2 diabetes to reduce diabetes complications.[3-5]

When beginning medical treatment, patients usually begin with a medication from one of six drug classes that have been approved by the Food and Drug Administration (FDA) for use as monotherapy, although several guidelines recommend use of metformin when not contraindicated as the first therapy after lifestyle modifications.[3, 4] The approved drug classes are metformin (alone in the biguanide class), sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Clinical guidelines, including those of the American Diabetes Association, recommend monitoring hemoglobin A1c (HbA1c) to determine the need for changing the medication dose or adding another agent to improve glycemic control.[4] Clinicians also monitor other intermediate outcomes, including body weight, and short-term and long-term safety and adverse effects of the drugs, which vary by drug class, with the goal of improving long-term clinical outcomes.

The Effective Health Care Program of the Agency for Healthcare Research and Quality (AHRQ) has published two prior systematic reviews comparing monotherapies and medication combinations for adults with type 2 diabetes.[6, 7] Since January 2010, the month of the last publications included in the past review, the FDA has approved one new medication class (SGLT-2 inhibitors, with 3 new medications) and several new DPP-4 inhibitors and GLP-1 receptor agonists. Additional data on previously approved medications have also emerged, which could change the balance of benefit and risk attributable to these drugs or could alter the strength of evidence about some of the drug comparisons previously reviewed.[8-11] Given the ever-increasing literature about type 2 diabetes medications and the recent approval of many new medications, an updated systematic review evaluating the effects of these medications on intermediate and long-term effectiveness and safety outcomes will be valuable to clinicians, patients, investigators, guideline developers, and payers.

Scope and Key Questions

This review updates the 2011 review on oral diabetes medications for adults with type 2 diabetes.[7] We are focusing on priority head-to-head drug class comparisons identified, a priori, as clinically relevant comparisons for which there are evidence gaps (Table A). Given the unique and emerging potential benefits and harms of some of these medications, we have included additional intermediate and safety outcomes in the review: for studies including either SGLT-2 inhibitors or GLP-1 receptor agonists, systolic blood pressure and heart rate, and for studies that

include a comparison with SGLT-2 inhibitors, impaired renal function, urinary tract infections, genital infections, volume depletion, and bone fractures.

The Key Questions that we address in this review are as follows:

Key Question 1a: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified monotherapy FDA-approved diabetes medications for the intermediate outcomes of HbA1c, weight, systolic blood pressure (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists), and heart rate (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists)?

Key Question 1b: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of metformin-based combinations of FDA-approved diabetes medications for the intermediate outcomes of HbA1c, weight, systolic blood pressure (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists), and heart rate (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists)?

Key Question 2a: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the monotherapy FDA-approved diabetes medications for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

Key Question 2b: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the metformin-based combinations of FDA-approved diabetes medications for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

Key Question 3a: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative safety of the monotherapy FDA-approved diabetes medications regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; and for comparisons including SGLT-2 inhibitors, what is the comparative safety regarding urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

Key Question 3b: In adults ages 18 or older with type 2 diabetes mellitus, what is the comparative safety of metformin-based combinations of FDA-approved diabetes medications regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; and for comparisons including SGLT-2 inhibitors, what is the comparative safety regarding urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

Key Question 4: Do the comparative safety and effectiveness of these treatments differ across subgroups defined by the age, sex, race/ethnicity, and body mass index of adults with type 2 diabetes?

Table A. Priority medication comparisons included for each Key Question

Intervention	Main Intervention Class (Generic Individual Drug Names)	Comparisons
Monotherapy as main intervention	Biguanides (metformin)	• Thiazolidinediones* • Sulfonylureas† • DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 receptor agonists‡ • Combination of metformin plus thiazolidinedione • Combination of metformin plus sulfonylurea • Combination of metformin plus DPP-4 inhibitor • Combination of metformin plus SGLT-2 inhibitor • Combination of metformin plus GLP-1 receptor agonist
	Thiazolidinediones (rosiglitazone or pioglitazone)	• Sulfonylureas • DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 receptor agonists
	Sulfonylureas (glimepiride, glyburide,¶ glibenclamide,¶ or glipizide)	• DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 receptor agonists
	DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, or sitagliptin)	• SGLT-2 inhibitors • GLP-1 receptor agonists
	SGLT-2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin)	• GLP-1 receptor agonists
Combination therapy as main intervention	Combination of metformin plus thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT-2 inhibitor or GLP-1 receptor agonist or basal insulin	• Combination of metformin plus sulfonylurea or DPP-4 inhibitor or SGLT-2 inhibitor or GLP-1 receptor agonist or basal insulin‡ or premixed insulin‡

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; SGLT-2 = sodium-glucose cotransporter 2.

*For studies comparing thiazolidinediones with metformin, we reviewed only HbA1c, long-term outcomes, and selected safety outcomes, given the high strength of evidence from our prior Comparative Effectiveness Review for other outcomes (specifically fracture and weight).[7]

† For studies comparing sulfonylureas with metformin, we reviewed only long-term outcomes and cancer, given the high strength of evidence on the other outcomes from our prior Comparative Effectiveness Review.[7]

‡ The generic individual drug names for the GLP-1 receptor agonists are exenatide, liraglutide, dulaglutide, and albiglutide. The generic individual drug names for basal insulin are insulin glargine, insulin detemir, and neutral protamine Hagedorn (NPH) insulin. The generic individual drug names for premixed insulin are NPH/regular 50/50, NPH/regular 70/30, insulin lispro 50/50, insulin lispro 75/25, and insulin aspart 70/30.

¶ Glyburide and glibenclamide are the same drug.

Methods

Topic Refinement and Review Protocol

This review updates the 2011 Comparative Effectiveness Review on diabetes medications for adults with type 2 diabetes.[7] We recruited a Technical Expert Panel (TEP) to review a draft of the protocol and a summary of the revisions from the 2011 review. The TEP included endocrinologists, general internists, biostatisticians, and representatives from government agencies. The TEP reviewed our protocol and provided feedback on the proposed methods for addressing the Key Questions. With the feedback from the TEP and the AHRQ representatives, we finalized and posted the protocol (www.effectivehealthcare.ahrq.gov).

Literature Search Strategy

Search Strategy

We searched MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL). We ran the search developed for the 2011 review with the date restrictions of April 2009 through April 2015. (See Appendix A.) The expanded search included medical subject headings (MeSH) and text words for all of the new medications included in this updated report, without date restrictions.

Additionally, we searched ClinicalTrials.gov to identify relevant registered trials. We reviewed the FDA Web site for any unpublished additional studies relevant to the topic as part of our gray literature search. We also provided an opportunity for manufacturers of interventions to submit unpublished data.

Study Selection

Two independent reviewers conducted title scans and advanced articles if either one thought them relevant. The abstract review phase was designed to identify studies reporting the effectiveness or safety of the medications and medication combinations of interest. Two investigators independently reviewed abstracts. Differences between investigators regarding the inclusion or exclusion of abstracts were resolved through consensus adjudication. Full articles underwent another independent parallel review regarding their appropriateness for inclusion. Selection criteria for studies are provided in Table B.

Table B. Study inclusion criteria

PICOTS	Inclusion Criteria
Population	• We included studies of adult humans with type 2 diabetes, non–insulin-dependent diabetes mellitus, or adult-onset diabetes.
Interventions	• We included studies that evaluated a diabetes medication of interest or drug combination of interest. (See Table A.)
Comparisons	• We included studies that evaluated a comparison of interest. (See Table A.)
Outcomes*	• We included studies addressing the following intermediate outcomes for KQ1: ▪ Hemoglobin A1c ▪ Weight ▪ Systolic blood pressure ▪ Heart rate • We included studies addressing the following microvascular, macrovascular, and mortality outcomes for KQ2: ▪ All-cause mortality ▪ Cardiovascular and cerebrovascular morbidity and mortality ▪ Retinopathy ▪ Nephropathy ▪ Neuropathy • We included studies addressing the following safety outcomes for KQ3: ▪ Liver injury ▪ Impaired renal function ▪ Lactic acidosis ▪ Pancreatitis ▪ Hypoglycemia ▪ Gastrointestinal side effects ▪ Congestive heart failure ▪ Cancer ▪ Macular edema or decreased vision ▪ Fractures ▪ Urinary tract infections ▪ Genital mycotic infections ▪ Volume depletion • KQ4 included studies considering any of the above outcomes.
Type of study	• For KQ1, we included only RCTs. • For KQ2 and KQ3, we included RCTs, nonrandomized experimental studies with a comparison group, and high-quality observational studies with a comparison group. • We included randomized trials that used a crossover design, with some exceptions. • Only studies published in English were included.
Timing and setting	We included studies in which the observed intervention or exposure period was more than 3 months.

KQ = Key Question; PICOTS = populations, interventions, comparisons, outcomes, timing, and settings; RCT = randomized controlled trial.
*Not every outcome was assessed for each comparison.

Data Extraction

Reviewers extracted information on the general study characteristics, study participant characteristics, interventions, comparisons, method of ascertainment of safety outcomes, and outcome results, including measures of variability. We also collected data on outcomes for the subgroups of interest, which were defined by age, sex, race/ethnicity, and body mass index.

Risk-of-Bias Assessment of Individual Studies

Two independent reviewers assessed risk of bias. We assessed the risk of bias in individual randomized controlled trials (RCTs) using the Jadad criteria, consistent with the prior report.[12] We used the Downs and Black tool for assessment of internal validity for nonrandomized trials and observational studies.[13] We included only medium- or high-quality observational studies, as

determined by assessment of each study's risk of bias. The Downs and Black tool was also applied to the observational studies that had been included in the prior report;[7] some of the previously included observational studies were excluded owing to methodological deficiencies.

Data Synthesis

For each Key Question, we created a set of detailed evidence tables containing all information extracted from eligible studies, including those from the prior Comparative Effectiveness Reviews. We conducted meta-analyses when there were sufficient data (at least 3 trials) and studies were sufficiently homogeneous with respect to key variables (population characteristics, study duration, and drug dose). We included in the quantitative pooling those study arms with drug doses and study durations most commonly reported. We tested the heterogeneity among the trials considered for quantitative pooling using a chi-squared test with a significance level of alpha less than or equal to 0.10, and we also examined heterogeneity among studies with an I^2 statistic.[14] We pooled the mean difference between groups using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity (I^2 <50%)[15] or the profile likelihood estimate when statistical heterogeneity was high.[16] For dichotomous outcomes, we calculated pooled odds ratios using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity[15] or the profile likelihood estimate in settings of high heterogeneity (I^2 >50%).[16] Sensitivity analyses included sequential study elimination to assess for influential studies. Stratification and metaregression (only if 10 or more studies were included in the meta-analysis) were done to identify and describe sources of heterogeneity and their effects on outcomes when substantial heterogeneity was identified.

Strength of the Body of Evidence

At the completion of the review, two reviewers sequentially graded the evidence addressing the Key Questions by adapting an evidence grading scheme recommended in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[17] We generated evidence grades about each intervention comparison for each outcome (Table A) for which there was at least one RCT or three observational studies. We graded the evidence separately for the RCTs and the observational studies.[17] The final evidence grade and conclusion were typically based on the RCT grade and could be strengthened by evidence from the observational studies. We separately assessed the strength of evidence for shorter and longer studies (≥2 years); however, we assessed strength of evidence only for longer studies from which we could draw a conclusion.

We assessed the study limitations, consistency, directness, precision, and reporting bias. If we conducted a meta-analysis for a body of evidence, we relied on the results of the meta-analysis to rate precision and used the designated minimally important differences as a point of reference for precision. (See full report for details.)

We classified evidence pertaining to the Key Questions into four categories: (1) high grade (indicating high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of the effect); (2) moderate grade (indicating moderate confidence that the evidence reflects the true effect, but further research could change our confidence in the estimate of the effect and may change the estimate); (3) low grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) insufficient (indicating evidence is unavailable or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion).

Applicability

We assessed the applicability of the evidence in terms of the degree to which the study populations, interventions, outcomes, timing, and settings were typical of the treatment of individuals with type 2 diabetes who are receiving treatment in a usual care setting, such as outpatient treatment by internists, family physicians, and endocrinologists.

Results

In this Executive Summary, results are presented by Key Question and focus on moderate- or high-strength evidence. We also highlight some key areas for which there was low-strength or insufficient evidence. The full results of this synthesis, including detailed results on all evidence, are in the full report.

Results of Literature Searches

We included 166 publications in our previous review. After excluding studies that no longer had a comparison or an outcome of interest and cohort studies that did not meet our quality criteria, we included 105 of these studies from the prior review (published in 107 articles) in the update.

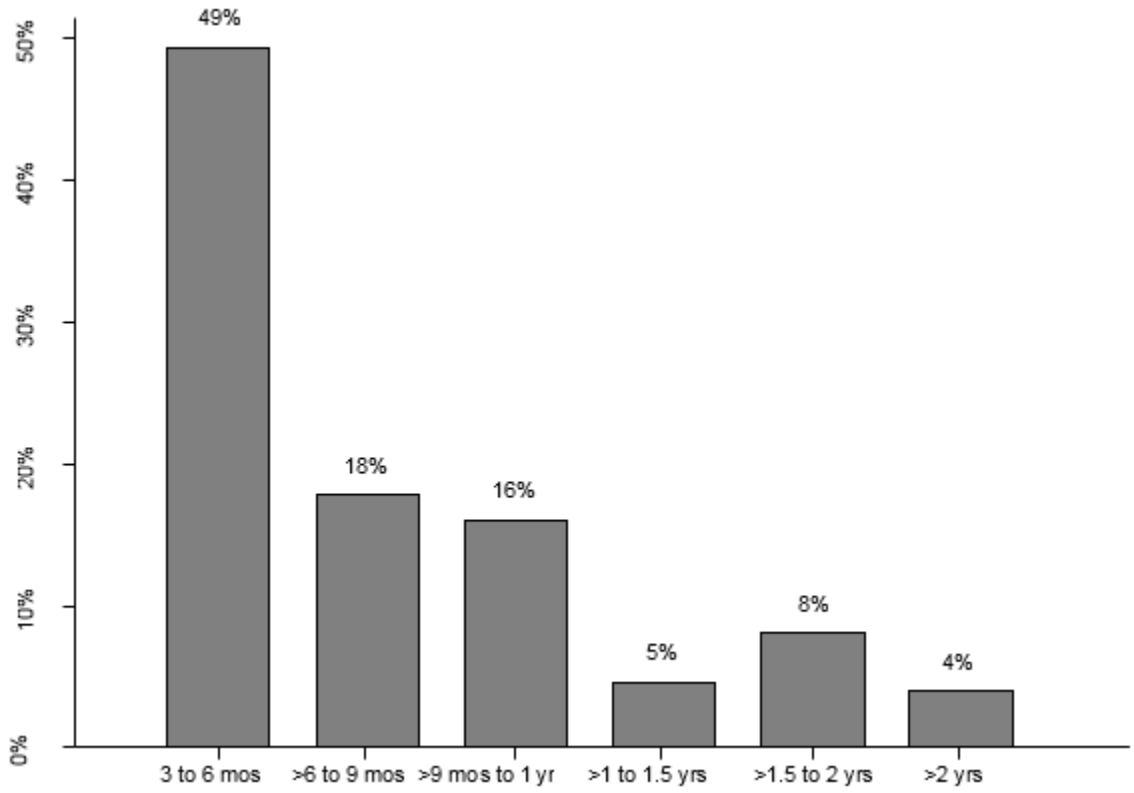
We also retrieved 19,171 unique citations from our updated literature search. After reviewing titles, abstracts, and full text, we included 114 new studies (published in 142 new articles). Ten of the new publications were either extensions or additional analyses of studies included in the previous review. Overall, we included 219 studies, published in 249 articles.

Study Duration for All Key Questions (KQ1–KQ4)

Of the 177 included RCTs for all Key Questions combined, most studies were less than 1 year in duration (Figure A). Only 4 percent of studies lasted longer than 2 years, making it difficult to draw any firm conclusions about long-term outcomes. Unless stated otherwise in the text or figures, results and conclusions for all the Key Questions are for short-term outcomes.

Followup among the 25 observational studies lasted between 3 months and 8 years. Five of the included observational studies lasted 1 year or less. Most (64%) of the cohorts had at least 2 years of followup.

Figure A. Duration of followup for randomized controlled trials comparing the effects of diabetes medications among adults with type 2 diabetes (N = 177)



Key Questions 1a and 1b: Intermediate Outcomes

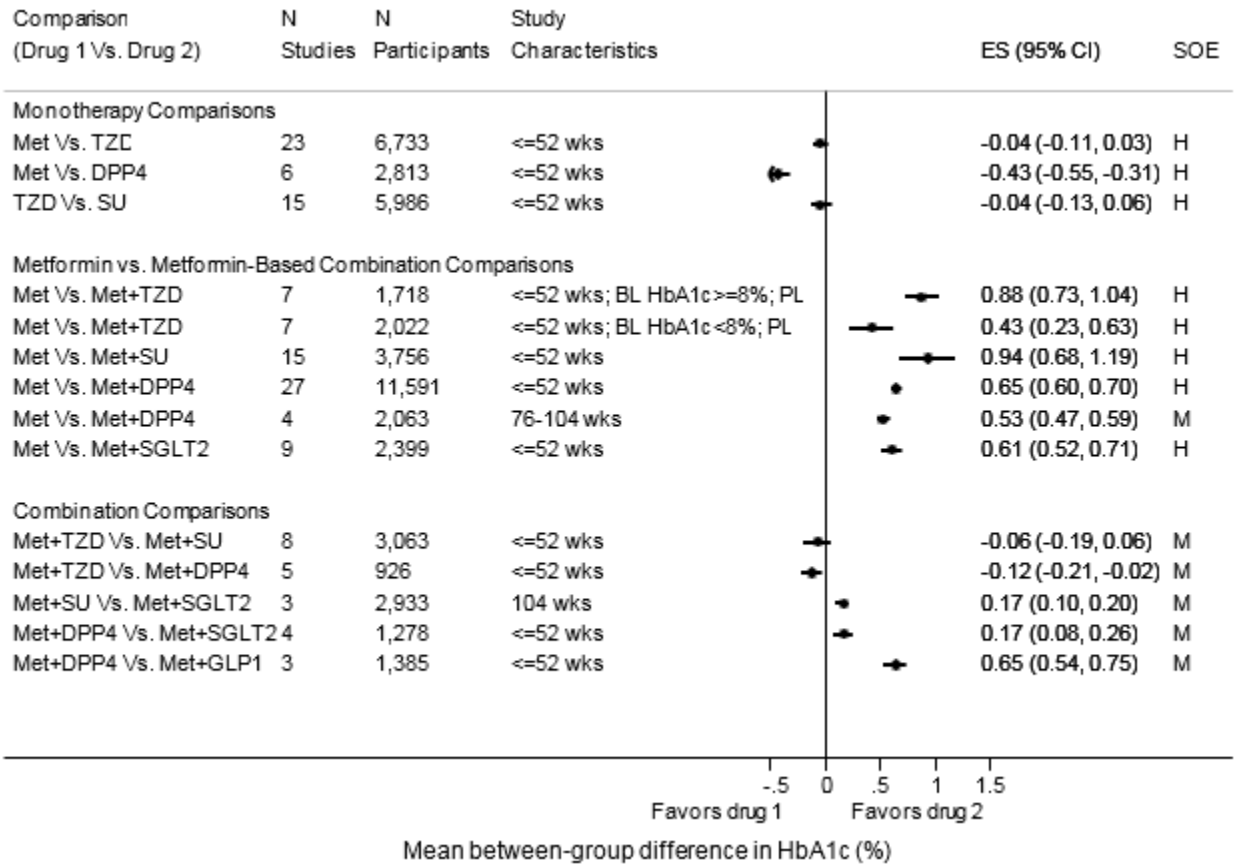
Of the 162 RCTs (reported in 189 articles) identified for Key Question 1, 81 percent were less than 1 year long. Only 12 percent of these trials reported having received no industry support, and 14 percent did not report on this at all. Study participants were generally overweight or obese and had a baseline HbA1c between 7 and 9 percent. The exclusion criteria were generally similar for most trials: significant renal, cardiovascular, and hepatic disease. About half of the trials (58%) excluded older subjects (generally older than 75 to 80 years of age). Almost all of the studies reported a diverse male-female mix among the participants. Of the few studies that evaluated longer timeframes (>2 years), most were consistent with the shorter term results. While an occasional longer study conflicted with the shorter study results, the high losses to followup (generally >20%) and frequent use of last observation carried forward analyses made it difficult to draw conclusions about longer term effects. Therefore, results discussed here are for the short term unless otherwise specified in the figures or text.

Hemoglobin A1c

We found that most diabetes medications as monotherapy (metformin, thiazolidinediones, and sulfonylureas) reduced HbA1c to a similar degree in the short term (Figure B). In the 2011 report,[7] the evidence on metformin versus sulfonylurea, which showed no significant between-group differences in HbA1c, was graded as high; therefore, the comparison was not updated in this report. In this report, metformin was more effective in reducing HbA1c than the DPP-4 inhibitors as monotherapy by about 0.4 percent. (All differences for HbA1c represent absolute

percentage points.) Two-drug combination therapies with metformin (such as metformin plus thiazolidinediones, metformin plus sulfonylureas, metformin plus SGLT-2 inhibitors, and metformin plus DPP-4 inhibitors) were generally more effective in reducing HbA1c than metformin monotherapy by about 1 percent (Figure B). For the combination comparisons, metformin plus a GLP-1 receptor agonist reduced HbA1c more than metformin plus DPP-4 inhibitors by 0.65 percent. Otherwise, most combination therapy comparisons with moderate strength of evidence had either no significant or no clinically meaningful between-group differences (<0.3%) in HbA1c between arms (Figure B). Although we included comparisons with the GLP-1 receptor agonists, we graded the evidence for most of these comparisons as insufficient or low; therefore, we were limited in our ability to draw conclusions about their effectiveness. Despite the clinical interest in comparing metformin plus injectables, there was insufficient or low strength of evidence on glycemic control for the following comparisons: metformin plus the GLP-1 receptor agonists versus metformin plus basal or premixed insulin, and metformin plus premixed insulin versus metformin plus basal insulin.

Figure B. Pooled between-group differences in hemoglobin A1c and strength of evidence for monotherapy and metformin-based combination comparisons



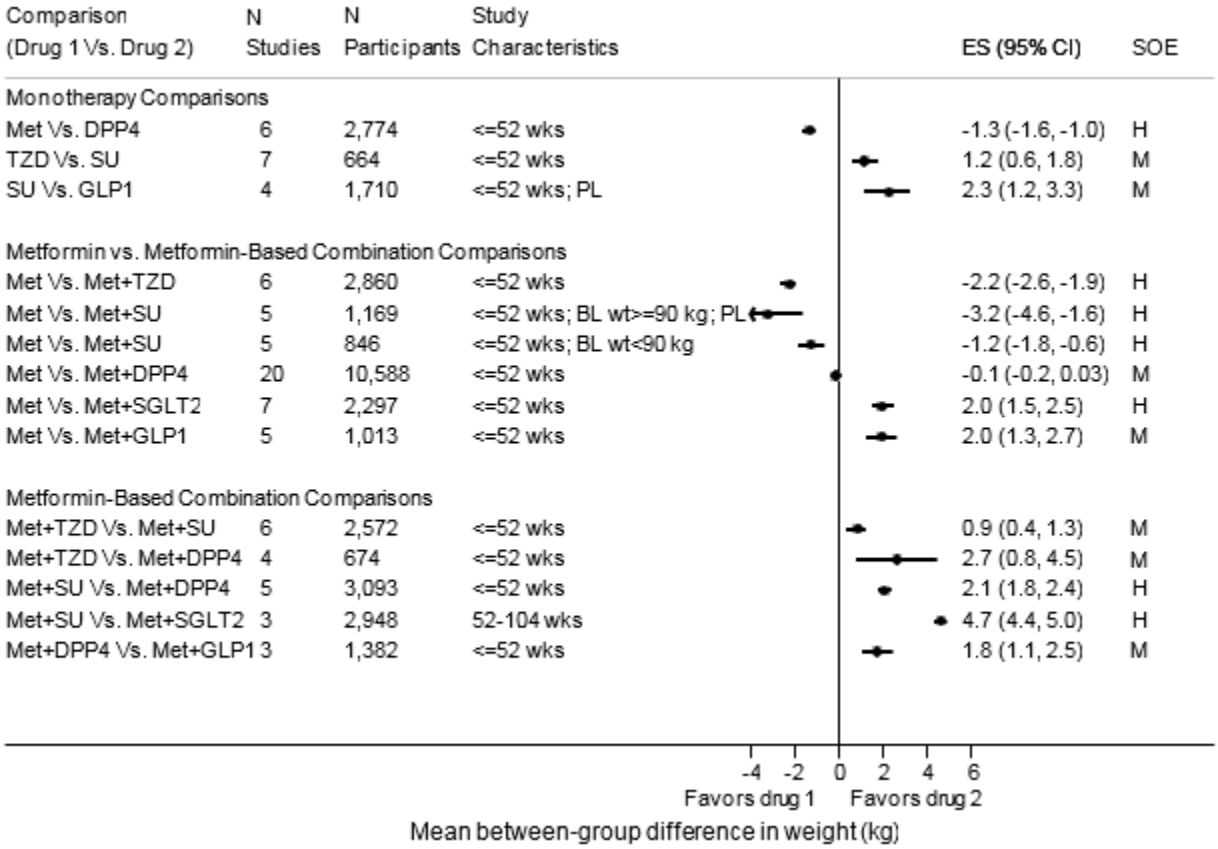
BL = baseline; CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (mean between-group difference in HbA1c); GLP1 = glucagon-like peptide-1 agonists; H = high; HbA1c = hemoglobin A1c; M = moderate; Met = metformin; PL = profile likelihood estimate; SGLT2 = sodium-glucose cotransporter-2 inhibitors; SOE = strength of evidence; SU = sulfonylurea; TZD = thiazolidinedione.
The width of the horizontal lines represents the 95% confidence intervals for each pooled analysis. Drug 1 is the reference group.

Weight

Monotherapy and combination medication comparisons generally showed significant between-group differences when comparing medications expected to increase weight (sulfonylureas, thiazolidinediones, and insulin) with medications expected to maintain or decrease weight (metformin, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors). Figure C shows the data from the meta-analyses that could feasibly be conducted. We report between-group differences in the text regarding results where meta-analyses could not be done. DPP-4 inhibitors and GLP-1 receptor agonists both decreased weight more than thiazolidinediones (between-group differences ranging from -2.3 kg to -3.5 kg). In the 2011 report, comparisons of metformin versus thiazolidinedione and metformin versus sulfonylurea were found to favor metformin by about -2.5 kg, with high strength of evidence; therefore, these comparisons were not updated.

In this report, several monotherapy and metformin-based combination medications were compared where both arms had medications expected to maintain or decrease weight, or both arms had medications expected to increase weight, with varying effects. Metformin decreased weight more than DPP-4 inhibitors, whereas sulfonylureas caused slightly less weight gain than thiazolidinediones (Figure C). There was moderate strength of evidence that SGLT-2 inhibitors decreased weight more than metformin and more than DPP-4 inhibitors (between-group differences ranging from -1.3 kg to -2.7 kg). The combinations of metformin plus a GLP-1 receptor agonist (Figure C) and metformin plus an SGLT-2 inhibitor (range in between-group differences of -1.8 to -3.6 kg) were both favored over the combination of metformin plus a DPP-4 inhibitor. Metformin plus a sulfonylurea had more favorable weight effects than the combination of metformin plus a premixed or basal insulin (range in mean between-group differences of -0.5 kg to -1.7 kg), with moderate strength of evidence. Despite the clinical interest in comparing metformin plus injectables, there was low strength of evidence about weight for the following comparisons: metformin plus the GLP-1 receptor agonists versus metformin plus basal or premixed insulin, and metformin plus premixed insulin versus metformin plus basal insulin.

Figure C. Pooled between-group differences in weight and strength of evidence for monotherapy and metformin-based combination comparisons



BL = baseline; CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (mean between-group difference in weight); GLP1 = glucagon-like peptide-1 agonists; H = high; M = moderate; Met = metformin; PL = profile likelihood estimate; SGLT2 = sodium-glucose cotransporter-2 inhibitors; SOE = strength of evidence; SU = sulfonylurea; TZD = thiazolidinedione.
The width of the horizontal lines represents the 95% confidence intervals for each pooled analysis. Drug 1 is the reference group.

Systolic Blood Pressure and Heart Rate

Systolic blood pressure and heart rate were evaluated only for the newer medications, SGLT-2 inhibitors and GLP-1 receptor agonists, owing to the suspected effects of these newer medications on these clinical outcomes based on prior literature.[18, 19] The SGLT-2 inhibitors consistently reduced systolic blood pressure by 3 to 5 mmHg in all comparisons for which there were sufficient numbers of studies (Table C). Also, metformin plus a GLP-1 receptor agonist yielded a greater reduction in systolic blood pressure, about 3 mmHg, compared with metformin alone (Table C).

For heart rate, only two comparisons had sufficient data to grade the evidence as more than insufficient or low. These comparisons had no or small differences (<2 beats per minute) between groups (Table C). When there were differences in outcomes among comparisons rated as having low strength of evidence, they were less than three beats per minute.

Table C. Summary of the moderate- to high-strength evidence on the comparative effectiveness and safety of diabetes medications as monotherapy and metformin-based combination therapy for systolic blood pressure and heart rate

Outcome	Conclusions	Strength of Evidence
Systolic blood pressure	Metformin plus an SGLT-2 inhibitor reduced systolic blood pressure more than— • Metformin alone: pooled between-group difference for shorter studies, 4.4 mmHg (95% CI, 2.9 to 6.0 mmHg) • Metformin plus SU: pooled between-group difference, 5.1 mmHg (95% CI, 4.2 mmHg to 6.0 mmHg)	High
	Metformin plus an SGLT-2 inhibitor reduced systolic blood pressure more than metformin plus a DPP-4 inhibitor: pooled between-group difference, 4.1 mmHg (95% CI, 3.6 mmHg to 4.6 mmHg).	Moderate
	SGLT-2 inhibitors reduced systolic blood pressure more than metformin: pooled between-group difference, 2.8 mmHg (95% CI, 2.6 mmHg to 3.0 mmHg).	Moderate
	Metformin plus a GLP-1 receptor agonist reduced systolic blood pressure more than metformin: pooled between-group difference, 3.1 mmHg (95% CI, 1.4 to 4.9 mmHg).	Moderate
Heart rate	Increases in heart rate were minimal and similar for metformin and GLP-1 receptor agonist monotherapy.	Moderate
	Combination therapy with metformin plus an SGLT-2 inhibitor resulted in less increase in heart rate than metformin plus an SU: pooled between-group difference in heart rate, 1.5 bpm; 95% CI, 0.6 bpm to 2.3 bpm.	Moderate

bpm = beats per minute; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylurea.

Key Questions 2a and 2b: All-Cause Mortality and Macrovascular and Microvascular Outcomes

Of 118 studies (reported in 141 publications) identified for Key Question 2, 96 were RCTs and 21 were observational (mainly retrospective cohort) studies. Most studies evaluated all-cause or cardiovascular mortality or cardiovascular morbidity. Of the 96 trials, 33 were at least 1 year in duration. Only 11 had 2 years or more of followup time, and 10 of these had over 20-percent losses to followup. No trial specified mortality or a macrovascular or microvascular outcome as its primary outcome. Mean/median followup of the observational studies ranged from 6 months to 5 years, with 12 lasting at least 2 years. Seven of the observational studies were designed to evaluate cardiovascular outcomes. Because of low event rates and sample size, the pooled studies for most comparisons on these outcomes were underpowered.

All-Cause Mortality, Cardiovascular Mortality, and Cardiovascular Morbidity

Only one comparison had moderate strength of evidence for any of these outcomes. The rest of the outcomes were rated as low strength of evidence or insufficient. We found moderate strength of evidence that sulfonylurea monotherapy was associated with a 50-percent to 70-percent higher relative risk (absolute risk difference, 0.1% to 2.9% in RCTs; number needed to treat, 20 to 1,000) of cardiovascular mortality compared with metformin monotherapy (Table D). This conclusion was supported by consistent findings from two high-quality RCTs (N = 4,664), with a range in mean/median followup of 2.8 to 4.0 years, and three high-quality observational studies (N =115,105) that used propensity score methodology (2 studies) and multivariate regression (1 study) to account for confounding. Our findings on all cause-mortality and cardiovascular morbidity, drawn from the same RCTs plus additional observational studies (noted in Table D), also favored metformin over sulfonylureas; however, the strength of

evidence was low for these outcomes because of less consistency in results across studies. It is of note that losses to followup were greater than 20 percent in both RCTs. Losses to followup were the same (20%) across arms in the study by Hong and colleagues (2013) and therefore not anticipated to bias the comparison of arms.[20] In A Diabetes Outcome Progression Trial (ADOPT), losses to followup were higher in the sulfonylurea (44%) than the metformin (38%) arm, with median followup of 3.3 years for the sulfonylurea arm versus 4.0 years for the metformin arm.[21] Therefore, study results were likely biased to the null, lending further support to the inference that metformin was favored over sulfonylurea monotherapy.

Table D. Comparative effectiveness of sulfonylureas compared with metformin for long-term all-cause mortality and cardiovascular mortality and morbidity—moderate strength of evidence or consistent low-strength evidence

Outcome	Range in RR From RCTs	Range in RD From RCTs	Adjusted HR From Observational Studies	SOE
All-cause mortality	1.0 to 2.1 (N = 2)	0.1% to 5.0% (N = 2)	1.2 to 1.9 (N = 7*)	Low
CVD mortality	1.5 to 1.7 (N = 2)	0.1% to 2.9% (N = 2)	1.1 to 1.6 (N = 3)	Moderate
CVD morbidity	0.7 to 1.4 (N = 2)	-10.1% to 0.4% (N = 2)	1.1 to 3.3 (N = 5†)	Low

CVD = cardiovascular disease; HR = hazard ratio; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SOE = strength of evidence.

*One additional retrospective cohort study reported an odds ratio of 1.1.

†Additionally, 1 case-control study reported an odds ratio of 1.2.

Retinopathy, Nephropathy, and Neuropathy

While we found more evidence than in the prior report, there were still too few studies to reach firm conclusions; all evidence for these outcomes was of low strength or insufficient.

Key Questions 3a and 3b: Comparative Safety

Of 145 studies identified for Key Question 3, 137 were RCTs and 8 were observational (mainly retrospective cohort) studies. Most RCTs lasted a year or less, with only about 5 percent lasting more than 2 years. Mean or median followup of the eight observational studies ranged from 3 months to 5 years. The few longer studies were generally consistent with the shorter term results; however, the losses to followup were often high (>20% in the majority of the longer studies), making it difficult to draw firm long-term conclusions. Therefore, most safety comparisons represent shorter term results unless specifically stated in the text or a figure.

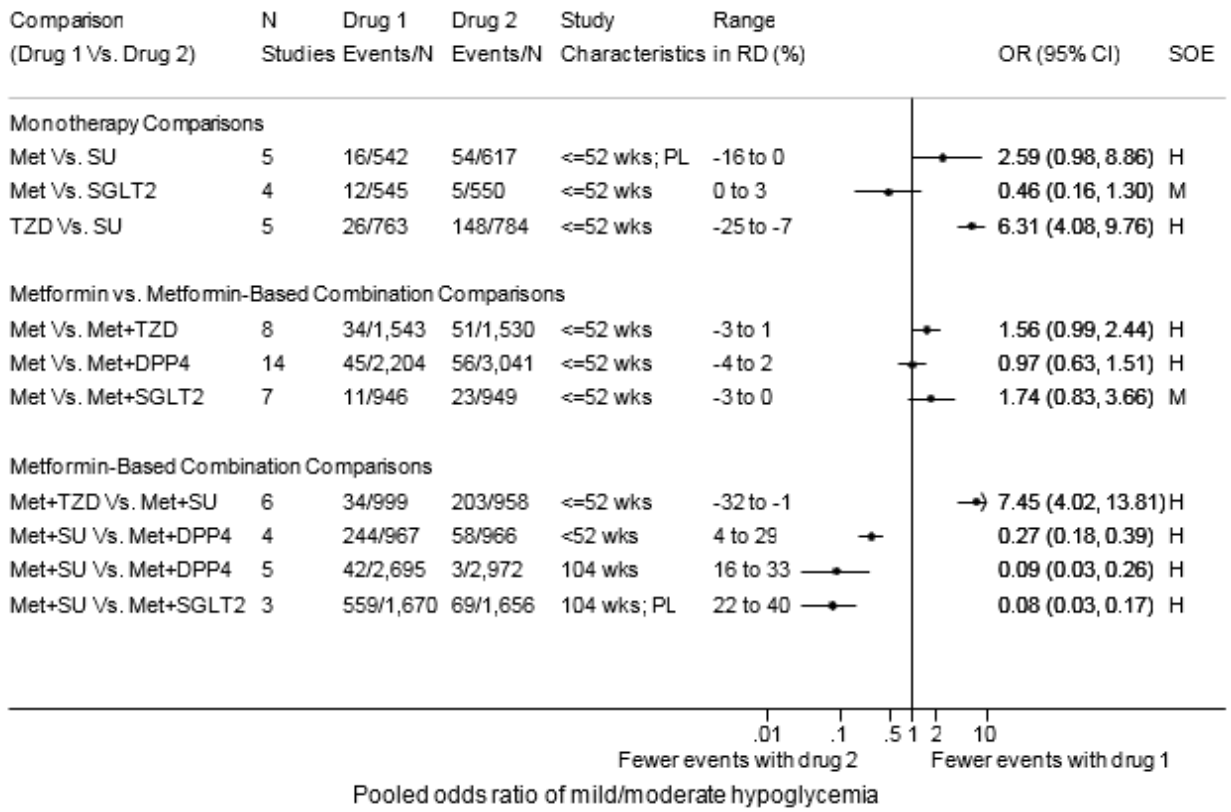
Hypoglycemia

Sulfonylureas alone and in combination with metformin had a higher risk of mild, moderate, or total hypoglycemia than any other monotherapies and metformin-based combinations for which we identified evidence (Figure D). While studies were too heterogeneous for a meta-analysis, sulfonylureas also had greater risk of hypoglycemia than GLP-1 receptor agonists (range in odds ratio [OR], 3.1 to 5.3; range in risk difference [RD], 12% to 21%) and DPP-4 inhibitors (range in OR, 3.8 to 12.4; range in RD, 6% to 15%), with moderate strength of evidence. In addition to the increased risk of hypoglycemia with metformin plus sulfonylurea versus several comparators (Figure D), the combination of metformin plus sulfonylurea also had greater risk of hypoglycemia compared with metformin monotherapy (range in OR, 2 to 17; range in RD, 0% to 35%) and compared with the combination of metformin plus a GLP-1 receptor agonist (for studies lasting 104 to 234 weeks: range in OR, 3.4 to 7.1; range in RD, 15% to 30%). When compared with metformin plus a basal or premixed insulin, metformin plus a

GLP-1 receptor agonist had less hypoglycemia risk (range in OR, 0.18 to 0.35; range in RD, -3% to -13%), with moderate strength of evidence. The combination of metformin plus basal insulin had a lower risk of hypoglycemia than the combination of metformin plus premixed insulin (range in OR, 0.23 to 0.89; range in RD, -5% to -28%), with moderate strength of evidence. We did not pool these studies owing to high heterogeneity.

We found moderate strength of evidence that sulfonylureas had an increased risk of severe hypoglycemia compared with metformin or thiazolidinedione monotherapy (range in OR, 1.4 to 8; range in RD, 0.5% to 23%). Similarly, sulfonylureas in combination with metformin had a greater risk of severe hypoglycemia than the combination of metformin plus DPP-4 inhibitors (range in OR, 6 to 14; range in RD, 0% to 3%) or metformin plus SGLT-2 inhibitors (OR, 7; range in RD, 1% to 3%), with moderate strength of evidence for both comparisons.

Figure D. Pooled odds ratios of mild/moderate hypoglycemia and strength of evidence for monotherapy and metformin-based combination comparisons



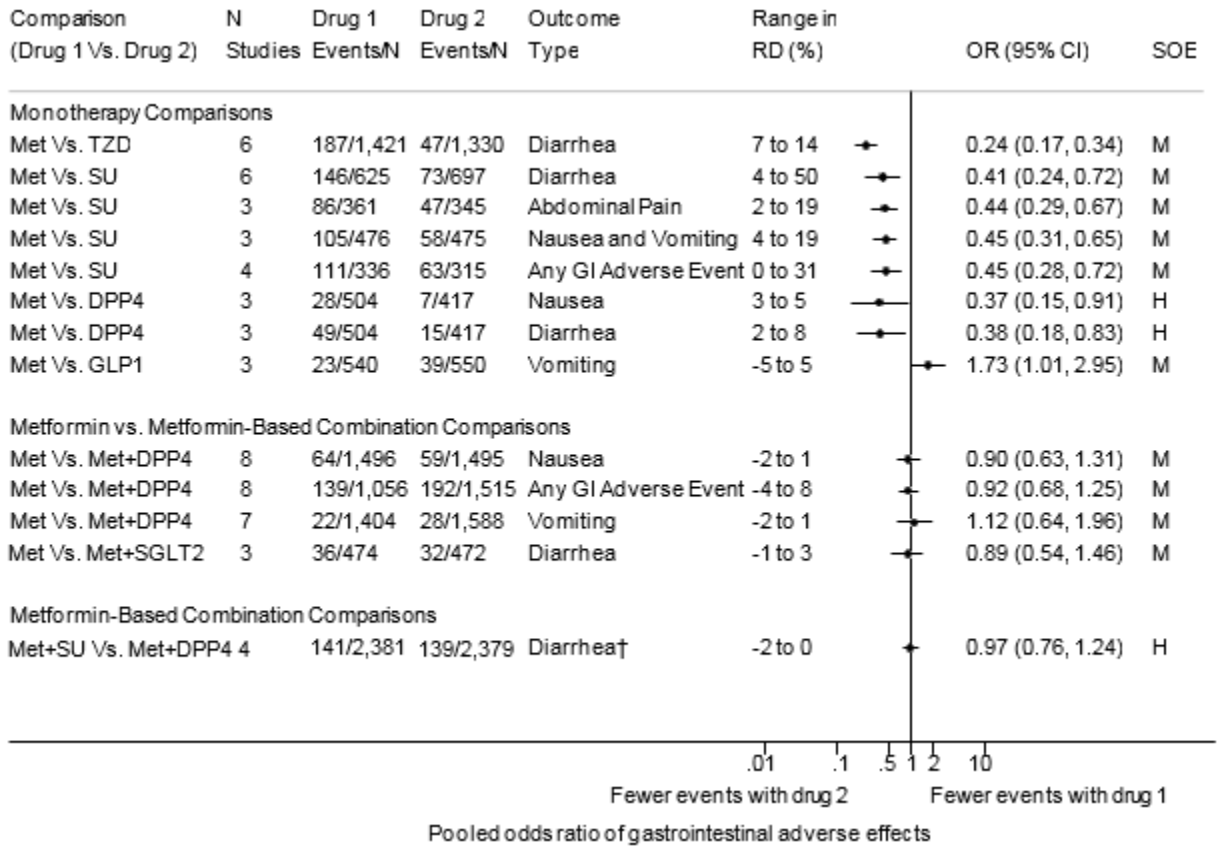
CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; H = high; M = moderate; Met = metformin; OR = odds ratio; PL = profile likelihood estimate; RD = absolute risk difference; SGLT2 = sodium-glucose cotransporter-2 inhibitors; SOE = strength of evidence; SU = sulfonylurea; TZD = thiazolidinediones.
The width of the horizontal lines represents the 95% confidence intervals for each pooled analysis. Drug 1 is the reference group.

Gastrointestinal Side Effects

Metformin and GLP-1 receptor agonists were associated with more gastrointestinal side effects (typically nausea, vomiting, or diarrhea) than any other medications with sufficient studies for comparison, regardless of whether they were used as monotherapy or in combination (Figure E). Although there were insufficient studies for a meta-analysis, GLP-1 receptor agonists

had greater gastrointestinal side effects than sulfonylureas, with moderate strength of evidence (range in OR, 1.4 to 2.4; range in RD, 3% to 9%). Metformin plus a GLP-1 receptor agonist had more gastrointestinal side effects than metformin plus DPP-4 inhibitors (range in OR, 1.0 to 7.7; range in RD, 0% to 23%) and metformin plus thiazolidinediones (range in OR, 2.9 to 6.3; range in RD, 8% to 19%), with moderate strength of evidence. Nausea and vomiting were more common with GLP-1 receptor agonists than with metformin (Figure E), but rates of diarrhea were similar between the groups. The rates of gastrointestinal side effects were similar for metformin monotherapy compared with metformin plus a DPP-4 inhibitor or metformin plus SGLT-2 inhibitors (Figure E). We found high strength of evidence that the rates of gastrointestinal adverse events were similar for thiazolidinediones (range, 2% to 9%) and sulfonylureas (range, 3% to 10%), with a range in RD of -1.2% to 1.7%. The combination of metformin plus a sulfonylurea (range, 1% to 18%) was also similar to the combination of metformin plus a thiazolidinedione (range, 1% to 13%), with a range in RD of -5.0% to 2.1% (moderate strength of evidence).

Figure E. Pooled odds ratios of gastrointestinal adverse events and strength of evidence for monotherapy and metformin-based combination comparisons*



CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1 receptor agonists; H = high; M = moderate; Met = metformin; OR = odds ratio; RD = absolute risk difference; SGLT-2 = sodium-glucose cotransporter-2 inhibitors; SOE = strength of evidence; SU = sulfonylurea; TZD = thiazolidinediones.
The width of the horizontal lines represents the 95% confidence intervals for each pooled analysis. Drug 1 is the reference group.
*All results presented in this graph are based on short-term (less than 52 weeks) studies unless otherwise specified.
†Based on studies with 104 weeks of followup.

Congestive Heart Failure

There was only one long-term trial, which lasted 4 years, and only a few observational studies of medium quality with 6 to 8 years of followup that allow an assessment of the comparative safety of diabetes medications regarding congestive heart failure. We found low strength of evidence that the risk of congestive heart failure was 1.2 to 1.6 times as great with thiazolidinediones as with sulfonylureas (pooled OR, 1.6; 95% CI, 0.96 to 2.8; range in RD, 0% to 2%) or metformin (2 RCTs lasting less than a year with no events; 1 4-year RCT with an RD of 3%; and range in hazard ratio of 1.2 to 1.5 in 2 observational studies). Despite recent concerns about congestive heart failure with specific DPP-4 inhibitors, we found low or insufficient strength of evidence on the comparative safety of this drug class for this outcome in studies lasting less than 2 years (5 RCTs reporting no events in the DPP-4 inhibitor arms; 1 RCT with 1 event in the metformin plus DPP-4 inhibitor arm and none in the comparator arm; and 1 RCT of metformin plus DPP-4 inhibitor vs. metformin plus sulfonylurea reporting fewer events in the DPP-4 combination arm compared with the sulfonylurea combination arm [3 vs. 6 events]).

Cancer

Evidence was generally lacking or of low strength for cancer outcomes. We found low strength of evidence that the combination of metformin plus a sulfonylurea was favored over the combination of metformin plus a DPP-4 inhibitor for cancer risk (3 RCTs with 104 weeks of followup). An unpublished study (104 weeks of followup) and an unpublished longer term (156 weeks) followup of one of the included published studies[22] were consistent with this finding and might have increased the evidence to moderate strength had they been included. A recent RCT with only 52 weeks of followup also found a higher risk of cancer in the DPP-4 inhibitor combination arm compared with the sulfonylurea combination arm.[23]

Adverse Events Specific to SGLT-2 Inhibitors

We evaluated the comparative effectiveness of SGLT-2 inhibitors for specific adverse events of interest: urinary tract infections, genital mycotic infections, renal function impairment, fractures, and volume depletion. We found high strength of evidence that the combination of metformin plus an SGLT-2 inhibitor increased the odds of a genital mycotic infection approximately threefold compared with metformin monotherapy and sixfold compared with the combination of metformin plus a sulfonylurea (Table E). We also found moderate strength of evidence that SGLT-2 inhibitors increased the odds of genital mycotic infection fourfold compared with metformin monotherapy. The evidence was of low strength or insufficient for the other safety outcomes specific to SGLT-2 inhibitors.

Other Outcomes

The evidence on the outcomes of liver injury, pancreatitis, lactic acidosis, severe allergic reactions, and macular edema and decreased vision was of low strength or insufficient. We could not make any conclusions about these outcomes.

Table E. Summary of the moderate- to high-strength evidence on the comparative safety of diabetes medications as monotherapy and metformin-based combination therapy for genital mycotic infections

Conclusions	Strength of Evidence

The rates of genital mycotic infections were higher with metformin plus SGLT-2 inhibitors compared with—
• Metformin monotherapy:
  ○ Pooled OR, 3.0; 95% CI, 1.2 to 7.2 for females
  ○ Pooled OR, 2.7; 95% CI, 0.8 to 9.0 for males
  ○ Range in between-group risk difference, -2.3% to 9.9%
• Metformin plus SU:
  ○ Pooled OR, 5.2; 95% CI, 3.4 to 8.0 for females
  ○ Pooled OR, 7.6; 95% CI, 4.0 to 14.4 for males
  ○ Range in between-group risk difference, 7.1% to 17.4%
	High

The rates of genital mycotic infections were higher with SGLT-2 inhibitors compared with metformin monotherapy
  ○ Pooled OR, 4.1; 95% CI, 2.0 to 8.3
  ○ Range in between-group risk difference, -0.04% to 15.7%
	Moderate

The rates of genital mycotic infections were higher with metformin plus SGLT-2 inhibitors compared with metformin plus DPP-4 inhibitors • Range in between-group risk difference, -2.8% to 8.8%	Moderate

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; OR=odds ratio; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylurea.

Key Question 4: Subgroups

We found little evidence on the comparative effectiveness and safety of diabetes medications in predefined subgroups of age, sex, race/ethnicity, or body mass index. Most of the evidence on subgroups was for the outcome of HbA1c and did not show differential effects of the included comparisons by age, sex, race/ethnicity, or body mass index.

Discussion

Key Findings in Context

Intermediate Outcomes

This report builds on prior work by adding more information for HbA1c and weight regarding the metformin-based combination comparisons and comparisons with the newer medications. It also adds new comparative information for the SGLT-2 inhibitors and GLP-1 agonists on both heart rate and blood pressure.

While there is controversy about HbA1c targets, better glycemic control (measured by HbA1c levels) is strongly associated with lower risk of microvascular disease,[24-26] making it a good proximal outcome to measure. Consistent with the 2011 Comparative Effectiveness Review, most monotherapies were found to be similarly effective in reducing HbA1c, with the exception of DPP-4 inhibitors, which had a smaller effect relative to metformin (Figure B).[7] While metformin versus GLP-1 receptor agonists and metformin versus SGLT-2 inhibitors also showed no clear between-group differences in HbA1c, the evidence was graded as low strength because the three studies in each comparison were imprecise and inconsistent. In this update, we found inconsistent findings in the studies of GLP-1 receptor agonists. It may be that the individual GLP-1 receptor agonists have different effects on HbA1c. A 2011 Cochrane systematic review showed small between-group differences in HbA1c, around 0.3 percent, favoring liraglutide and weekly exenatide over daily exenatide.[19]

Combination therapy with metformin generally reduced HbA1c by 0.7 to 1 absolute percentage points compared with metformin monotherapy. While we found moderate strength of evidence that some combination comparisons were more effective than others, most between-group differences were small (<0.3 percentage points), with questionable clinical relevance. Only one combination comparison with moderate strength of evidence was favored by greater than 0.3 percentage points over any other combination comparison: the combination of metformin plus a GLP-1 receptor agonist reduced HbA1c more than metformin plus a DPP-4 inhibitor by 0.65 percentage points. Two prior network meta-analyses[27, 28] showed that most metformin combination comparisons had similar reductions in HbA1c. However, the results of the direct comparisons evaluated in this report are more precise, allowing us to detect smaller between-group differences than the indirect comparisons in the network meta-analyses.

Weight gain was small to moderate in the trials in which participants gained weight; even in the longest trials, weight gain was less than 5 kg. However, even small to moderate weight gain (5% to 10% of body weight) may be associated with increased insulin resistance.[29] In addition, weight loss and glycemic control were reported as the primary drivers of patient preferences for diabetes medications when compared with treatment burden and side effects in a recent systematic review.[30] Drug effects on weight, therefore, have a strong impact on the choice of the drug for second-line combination therapy in a patient not well controlled on a single agent. Our

systematic review builds on prior work by adding more direct comparative data about metformin combination comparisons that further confirm the known weight effects of the individual medications. As monotherapy and in combination with metformin, thiazolidinediones, sulfonylureas, and insulin are associated with weight gain, DPP-4 inhibitors with weight maintenance, and SGLT-2 inhibitors and GLP-1 receptor agonists with weight loss.[7, 18, 19, 31]

We evaluated systolic blood pressure and heart rate for the newer classes of medications, the SGLT-2 inhibitors and GLP-1 receptor agonists, because of suspected effects of these medications based on prior literature.[18, 19] Blood pressure control is essential in adults with diabetes.[32-35] The United Kingdom Prospective Diabetes Study showed that for every 10 mmHg decrease in systolic blood pressure, there is a 15-percent decrease in diabetes-related deaths.[33] Our findings of modest systolic blood pressure reductions of 3 to 5 mmHg with SGLT-2 inhibitors compared with many other agents are consistent with other reviews[18] on these agents, and our review builds on prior work by evaluating direct comparisons of specific medication classes. This is important because thiazolidinediones and GLP-1 receptor agonists have been associated previously with decreases in systolic blood pressure of 3 to 5 mmHg.[6, 19] We also found moderate strength of evidence that metformin plus a GLP-1 receptor agonist had a greater reduction in systolic blood pressure than metformin alone (pooled between-group difference, 3.1 mmHg; 95% CI, 1.4 to 4.9 mmHg). While the clinical relevance of these small differences is unclear, a change of 3 to 5 mmHg is about half the effect of a low-sodium diet (around 7 to 11 mmHg) and about one-third the effect of blood pressure medications (around 10 to 15 mmHg).[36, 37] Future research should determine if there are any links between these small differences in blood pressure and micro- and macrovascular outcomes, especially given the prevalent use of effective medications to reduce cardiovascular risk (e.g., aspirin, blood pressure and cholesterol medications).

Increased heart rate is associated with increased mortality.[38] However, whether heart rate is an independent predictor of long-term clinical outcomes, such as mortality, is less clear.[39] We wanted to determine if the potential benefits from blood pressure reduction might be offset by a concomitant increase in heart rate. We did not identify any prior systematic reviews that evaluated this outcome for the diabetes comparisons of interest. Only two comparisons had sufficient data to grade the evidence as more than insufficient or low. The SGLT-2 inhibitors in combination with metformin were found to decrease heart rate by 1.5 beats per minute (bpm) (95% CI, 0.6 bpm to 2.3 bpm) when compared with metformin plus a sulfonylurea; metformin and GLP-1 receptor agonists showed no differences in heart rate between groups. Therefore, these early findings support minimal to no effects on heart rate and no increase in heart rate for the newer medications.

All-Cause Mortality and Macrovascular and Microvascular Outcomes

Additional evidence allowed this report to include firm conclusions regarding metformin versus sulfonylurea monotherapy for cardiovascular mortality. Sulfonylurea monotherapy was associated with a 50-percent to 70-percent higher relative risk of cardiovascular mortality than metformin monotherapy (for sulfonylurea vs. metformin: absolute risk difference, 0.1% to 2.9%; number needed to harm, 34 to 1,000 in RCTs). The low-strength evidence regarding all-cause mortality and cardiovascular morbidity was consistent with this conclusion, also favoring metformin over sulfonylureas. Our results augment findings from prior meta-analyses published in 2012 and 2013, which relied more heavily on observational data or did not report on explicit head-to-head comparisons of metformin and sulfonylurea monotherapy.[40, 41] Importantly, we do

not know if metformin actually decreases cardiovascular disease mortality or just increases cardiovascular disease mortality less than sulfonylureas; likewise, we do not know if sulfonylureas actually increase cardiovascular disease mortality or just decrease cardiovascular disease mortality less than metformin.

We did not find evidence to support substantive conclusions about the comparative effectiveness of thiazolidinediones on long-term cardiovascular risk and therefore could not address the issues raised previously about rosiglitazone and cardiovascular outcomes.[42] We did not include the Rosiglitazone Evaluated for Cardiovascular Outcomes in oral agent combination therapy for type 2 Diabetes (RECORD) Trial here because it did not report on macrovascular outcomes stratified by specific medication combinations of interest; however, a reanalysis of data from this study led the FDA to lift its restrictions on the use of rosiglitazone.[43]

We found little evidence supporting conclusions regarding the comparative effectiveness of most of the newer classes of drugs (DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors) and these clinical outcomes. However, three recent large placebo-controlled RCTs not meeting our inclusion criteria (because they did not evaluate direct head-to-head comparisons of interest) evaluated the effects of DPP-4 inhibitors on cardiovascular outcomes: SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction) 53, EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care), and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin). These studies reported noninferiority for DPP-4 inhibitors relative to standard care,[44-46] but several limitations prevent conclusions based on these studies: (1) differential diabetes medication use across arms; (2) low power to demonstrate noninferiority; and (3) mixed inconsistent findings on cardiovascular outcomes across trials (N >35,000).[44-46]

Otherwise, most of the evidence on all-cause mortality and macrovascular and microvascular outcomes came from RCTs that were generally 12 months or shorter in duration with rare or no events; this evidence was of low strength or insufficient, precluding conclusions on the comparative effectiveness of the comparisons of interest for short-term harms. The scant evidence on the comparative effectiveness of diabetes medications and microvascular outcomes (retinopathy, nephropathy, and neuropathy) precluded any substantive conclusions.

Safety Outcomes

Severe hypoglycemia is associated with increased morbidity (e.g., reduced cognition), increased avoidable health care use (e.g., emergency room visits for hypoglycemia), and increased mortality.[47-50] In this report, we confirmed the elevated risk for severe hypoglycemia and nonsevere hypoglycemia with sulfonylureas compared with other drug classes (Figure D).We added to the literature base on SGLT-2 inhibitors by providing more evidence showing that SGLT-2 inhibitors may have less risk of hypoglycemia than metformin, although both medications had low absolute rates of hypoglycemia. We also found that, when compared with metformin plus basal or premixed insulin, metformin plus a GLP-1 receptor agonist had less hypoglycemia risk.

For the outcome of gastrointestinal side effects, we also confirmed findings from our 2011 report[7] and a prior Cochrane systematic review[19] that both metformin and GLP-1 receptor agonists induce more gastrointestinal side effects than most comparators. Our data add information about specific combination comparisons and specific types of gastrointestinal adverse events. The combinations of metformin plus DPP-4 inhibitors did not have worse

gastrointestinal side effects than metformin monotherapy or metformin plus a sulfonylurea. We identified new evidence about GLP-1 receptor agonists and SGLT-2 inhibitors: metformin plus a GLP-1 receptor agonist was associated with more gastrointestinal side effects than metformin plus a thiazolidinedione or metformin plus a sulfonylurea. GLP-1 receptor agonists were associated with more vomiting, but similar rates of diarrhea, when compared with metformin monotherapy. SGLT-2 inhibitors did not increase gastrointestinal side effects when added to metformin.

There was only one long-term trial lasting 4 years (the rest, less than 2 years) and only a few observational studies of medium quality with 6 to 8 years of followup that assessed the effect of diabetes medications on congestive heart failure. We found 1.2 to 1.6 times increased odds of heart failure with the thiazolidinedione class of medications (low strength of evidence) when compared with metformin or sulfonylureas, a finding also reported in two recent meta-analyses.[51, 52] We excluded the RECORD study for this outcome because the active comparator in the analysis was either sulfonylurea or metformin instead of a single active comparator. Consistent with our findings, RECORD showed that the combination of thiazolidinediones and another agent (sulfonylurea or metformin) was associated with a significant doubling in the risk of heart failure compared with the combination of sulfonylurea and metformin.[53] Both thiazolidinediones, rosiglitazone and pioglitazone, are contraindicated in patients with serious or severe heart failure (Stage 3 or Stage 4) according to product labels.[54, 55]

We had low or insufficient strength of evidence for most other medication comparisons for heart failure, including the newer agents. Despite recent concerns about congestive heart failure with DPP-4 inhibitors, we found low or insufficient strength of evidence on the comparative safety of this drug class for this outcome in mainly short studies. Several large double-blind placebo-controlled RCTs evaluating DPP-4 inhibitors on cardiovascular outcomes in adults with moderate to high cardiovascular risk were excluded from our systematic review of head-to-head comparisons but deserve mention because of recent controversy.[44-46] Two of these RCTs (comparing either saxagliptin or alogliptin with placebo) reported an increased risk of hospitalization for congestive heart failure in adults at moderate to high cardiovascular risk (range in RD of 0.7% and 0.9%).[44, 46] The EXAMINE trial with alogliptin reported these differences solely for the outcome of first hospitalization for heart failure in adults without preexisting congestive heart failure as part of a post hoc subgroup analysis.[46] The third placebo-controlled RCT[45] compared sitagliptin with placebo on cardiovascular outcomes in adults at elevated risk for these outcomes, and reported no between-group differences in hospitalization for congestive heart failure (3.1% in each arm). It is unclear if differences in these trials result from differences in drug type, chance alone, or other causes. Because of these findings, however, the FDA has requested additional labeling for saxagliptin and alogliptin to reflect concerns about the potential increased risk of hospitalization for congestive heart failure.[56] Further research directly comparing specific DPP-4 inhibitors with other active comparators and placebo will be useful in determining the comparative safety of these medications on heart failure risk. Two RCTs of linagliptin are in progress: the Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) and the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) studies.[57, 58]

As in the 2011 report,[7] we found little evidence about cancer risk. While animal studies have raised concerns about medullary thyroid cancer with GLP-1 receptor agonists[59-62] and in vitro studies have raised concern about pancreatic cancer risk with incretin mimetic therapies,[63] we

found no evidence allowing for substantive conclusions on the association between GLP-1 receptor agonists or DPP-4 inhibitors and cancer. We found low strength of evidence from published RCTs with 104 weeks of followup that the combination of metformin plus a sulfonylurea was favored over the combination of metformin plus a DPP-4 inhibitor for cancer risk; unpublished studies that supported these findings may have strengthened this evidence if they had been included in our review. A newer study with only 52 weeks of followup also corroborated the findings from the longer RCTs. The SAVOR-TIMI 53, TECOS, and EXAMINE trials, mentioned earlier, did not find differences in the risk of pancreatic cancer for DPP-4 inhibitors added to current treatment versus standard care, but other diabetes medication use was differential across arms, thus limiting inferences about effects specific to DPP-4 inhibitors.[44-46] Reviews and meta-analyses suggest that metformin decreases the risk of many types of cancer[64, 65] and that pioglitazone[66] increases the risk of bladder cancer slightly, but we could not include many of the studies supporting those conclusions in our review because of our stringent inclusion criteria for observational studies.

We found little evidence from comparative effectiveness studies to substantiate firm conclusions about the risk of pancreatitis for DPP-4 inhibitors and GLP-1 receptor agonists, since we excluded placebo-controlled trials and studies that did not include the specific diabetes medication comparisons of interest for this review. SAVOR-TIMI 53, TECOS, and EXAMINE all reported increased incidence of acute pancreatitis with DPP-4 inhibitors added to standard therapy versus standard therapy alone, with a consistent risk difference of 0.1 percent (number needed to harm for DPP-4 inhibitors, 1,000).[44-46] Data across the Liraglutide Effect and Action in Diabetes (LEAD) RCTs also found more pancreatitis with DPP-4 inhibitors.[67]

We have added additional evidence on specific comparisons based on SGLT-2 inhibitors, confirming the increased risk of genital mycotic infections with this class, which has been described in prior reviews.[18, 68] The evidence on SGLT-2 inhibitor comparisons regarding fractures, renal impairment, urinary tract infections, and volume depletion was not conclusive. However, in late 2015, the FDA strengthened its warning of an increased risk of fractures with canagliflozin based on pooled data from nine clinical trials (mean followup, 85 weeks) that showed incidences of fracture of 1.4 and 1.5 per 100 patient-years for canagliflozin 100 mg daily and canagliflozin 300 mg daily, respectively, versus 1.1 per 100 patient-years for the active/placebo combined comparators.[69] The labeling for canagliflozin notes that factors that increase fracture risk should be considered when starting canagliflozin.[70]

The FDA issued a warning on the possible risk of ketoacidosis associated with SGLT-2 inhibitors on May 15, 2015.[71] We did not evaluate this outcome, because it was not a concern at the time of the selection of outcomes for this report; the FDA has not changed the labeling for SGLT-2 inhibitors and is currently evaluating emerging data on this issue. A separate analysis of 17,596 participants in canagliflozin trials showed a dose-dependent increased risk of ketoacidosis in participants receiving SGLT-2 inhibitors versus other therapy/placebo; the authors noted that a number of patients with ketoacidosis had evidence of autoimmune diabetes.[72]

Evidence on other adverse events, including liver injury, lactic acidosis, macular edema or decreased vision, and severe allergic reactions, does not support conclusions. Similarly, the evidence on the comparative effectiveness of diabetes medications in subgroups defined by age, sex, race/ethnicity, and body mass index was generally insufficient for conclusions.

Implications

This update provides additional evidence supporting metformin as the firstline medication therapy to treat type 2 diabetes when tolerated, and it supports a number of treatment options that might be added to metformin based on patient preferences. Not only is metformin favored on many intermediate outcomes, including HbA1c and weight, but also we found more conclusive evidence that cardiovascular mortality is higher with sulfonylureas than metformin. This is consistent with several guidelines, such as those of the American College of Physicians and American Diabetes Association, which recommend metformin as a firstline treatment choice.

The alternative to initial therapy with metformin in type 2 diabetes is an important consideration, given that metformin is not currently recommended for use in patients with kidney disease[73] (approximately 22% of people with diabetes in the United States)[74] or may not be tolerated because of side effects. In addition, the "best" second-line therapy after metformin is still unclear. We evaluated non–metformin-based monotherapy comparisons in this report and demonstrated that the other monotherapies, with the exception of DPP-4 inhibitors, which are not as effective in reducing HbA1c as metformin, generally decrease HbA1c to a similar extent (and comparably to metformin). These other monotherapies' effects on body weight vary, as do their risks, such as congestive heart failure (increased risk for thiazolidinediones), hypoglycemia (highest risk with sulfonylureas, including for severe hypoglycemia for many comparisons), gastrointestinal side effects (nausea and vomiting with GLP-1 receptor agonists), and genital mycotic infections (increased risk for SGLT-2 inhibitors). Most importantly, we do not have conclusive evidence on the relative long-term effects of non–metformin-based monotherapy comparisons on all-cause mortality or cardiovascular outcomes, microvascular outcomes, and rare serious adverse events (e.g., pancreatitis risk with GLP-1 receptor agonists). The evidence we present on metformin-based combination therapies provides some insight into the selection of add-on therapy to metformin, but it is not definitive because of the uncertainty of long-term outcomes and differential effects on weight and adverse effects. Comparisons of the metformin-based combinations yielded effectiveness and safety results consistent with the metformin monotherapy comparisons described in detail previously. Therefore, the "best" alternative to metformin initial therapy or the "best" second-line therapy choice after metformin remains unclear and should be based on individual patient factors, as suggested in recent guidelines.[4] These include clinical factors such as patient age and weight as well as preferences related to differential effects of medications on weight, hypoglycemia, and gastrointestinal and other side effects; tolerance of unknown risks; treatment burden (e.g., oral vs. parenteral administration); and cost.

Limitations of the Review Process

A few key limitations to our review deserve mention. To focus on comparative effectiveness, we did not include placebo-controlled studies and instead evaluated head-to-head comparisons. We also excluded studies in which participants could take nonstudy drugs for treating diabetes ("background" medications) and the results were not stratified by medication. We used this exclusion to avoid interactions between medications. This was especially important because of our goal of evaluating two-drug combinations. Using these criteria, we excluded several large trials,[26, 47, 75-83] because investigators did not stratify their results to allow reporting on the head-to-head comparisons of interest. We also used strict selection criteria for observational studies, mainly based on the control of confounding factors. In this way, we included observational

studies with the most valid results to support conclusions. Also, we focused on interclass (and not intraclass) comparisons in this report. While we did not combine studies in which individual drugs were found to be a clinical or statistical source of heterogeneity, we may have missed smaller intraclass differences. In our 2007 report,[6] we found that glyburide/glibenclamide had a higher absolute risk difference of mild, moderate, or total hypoglycemia than other sulfonylureas (pooled RD, 3%; 95% CI, 0.5% to 5%). In this update, which focused on interclass comparisons, the studies that included glyburide/glibenclamide as the sulfonylurea did not consistently have larger between-group differences in hypoglycemia risk than the other sulfonylurea studies. Therefore, these studies were combined with the other sulfonylurea comparisons for hypoglycemia evaluation. For microvascular outcomes, we included studies evaluating more proximal measures, such as change in retinal exam or changes in microalbuminuria, which may be less relevant than other included clinical outcomes of blindness and changes in estimated glomerular filtration rate. However, we were unable to conclude anything about comparative effects on the microvascular outcomes because of lack of sufficient evidence. These distinctions may become more important as more evidence accrues on the different microvascular outcomes. Finally, we did not evaluate patient-reported outcomes, such as quality of life; future research is needed to identify ideal measures to assess treatment-sensitive patient-reported outcomes in diabetes.

Applicability

Using the PICOTS (populations, interventions, comparisons, outcomes, timing, and setting) framework, the evidence in this report is generally applicable to the population of U.S. adults with type 2 diabetes, with a few notable concerns. Compared with the general population with type 2 diabetes,[84] populations in the included studies had fewer elderly adults (e.g., often excluded persons ≥75 years of age), had fewer significant comorbid conditions, and were less racially and ethnically diverse. Regarding the interventions, the majority of studies were less than 2 years long, while patients with diabetes are typically on medications for decades. While many of the longer duration studies were consistent with the short-term findings, more studies lasting longer than 2 years are needed to better understand the durability of the differences reported in shorter term studies.

Research Gaps

Based on the limitations of the evidence base, we highlight several major gaps in the evidence using the PICOTS framework and provide corresponding recommendations for future research (Table F).

The most important gap is the lack of conclusive evidence on the comparative effectiveness and safety of the diabetes medications for all-cause mortality, macrovascular complications, microvascular complications, and rare serious adverse events. Based on the relatively low frequency of these outcomes and long timeframe for development, RCTs are simply not feasible to address this gap because of both cost and the need for evidence now (and not in 5 to 10 years). Therefore, supplementing the rare RCT that can be conducted for these outcomes with high-quality observational studies is paramount.

Database requirements for such observational studies include sufficient sample size, followup of patients over time, detailed data on treatments (including doses and duration), and detailed data on confounding variables (e.g., duration of diabetes, comorbid conditions). Study designs will need to handle the following sources of bias: confounding by indication, immortal

time bias, time- and cumulative exposure-varying incidence of outcomes, reverse causation, informative censoring, time-varying drug exposure, and time-dependent confounders.[85]

Table F. Evidence gaps and future research needs for the comparative effectiveness and safety of diabetes medications for adults with type 2 diabetes

Category	Evidence Gap	Future Research Needs
Population	• Lack of study of older adults, racial/ethnic minorities, and people with comorbid conditions, such as significant renal, cardiovascular, and hepatic impairment • Limited evidence on a priori subgroups of interest, such as older adults, racial/ethnic minorities, and subgroups by sex and BMI	• Studies that include diverse populations • Studies with an a priori plan to investigate differences by important subgroups of interest
Interventions and comparators (HbA1c, weight, hypoglycemia, and GI adverse events)	• Limited information on GLP-1 receptor agonist comparisons as monotherapy and in combination with metformin • Limited information on metformin plus insulin vs. other metformin-based combinations	• RCTs evaluating the GLP-1 receptor agonists as monotherapy and in combination with metformin • RCTs evaluating metformin plus insulin with other metformin-based combinations, especially metformin plus GLP-1 receptor agonist as injectable add-on therapy to metformin
Outcomes		
All-cause mortality and macrovascular and microvascular outcomes	• Limited information on macrovascular outcomes and death • Underpowered existing evidence • Limited number of high-quality observational studies • No conclusive evidence on microvascular outcomes • No RCTs evaluating these outcomes as a primary outcome • Inconsistent outcome definitions, ascertainment, and reporting in each study arm	• High-quality observational studies* for all comparisons • Longer duration RCTs (>2 years) for all comparisons evaluating macrovascular and microvascular events as primary outcomes • Standardized definitions for macrovascular and microvascular outcomes • Reporting on outcomes in all arms of RCTs

Rare safety outcomes	• Limited evidence on rare safety outcomes
	• Underpowered existing evidence
	• Lack of high-quality observational studies
	• Inconsistent outcome definitions, ascertainment, and reporting in each study arm, especially for pancreatitis and cancer
		• High-quality observational studies*
		• RCTs—
		  ○ Active ascertainment of all safety outcomes
		  ○ Standardized definitions for all safety outcomes
		  ○ Reporting on safety outcomes in all arms
		  ○ Responsiveness to incorporating evaluation of new safety concerns

Timing	• Most evidence is for short-term outcomes, as few studies lasted more than 2 years	• Longer duration studies (>2 years) to—
		  ○ Determine durability of short-term comparative effects on HbA1c and weight
		  ○ Determine long-term clinical effectiveness and safety

Methodological	• High, and often differential, losses to followup in RCTs • Lack of reporting on randomization methods for RCTs • Lack of reporting on allocation concealment, blinding, and withdrawals for all studies • Lack of appropriate accounting for bias in observational studies • Lack of reporting on treatments in observational studies	• Complete or near-complete followup in RCTs • Appropriate methods to account for losses to followup in RCTs • Reporting on methods for randomization, allocation concealment, and blinding in RCTs • High-quality observational studies* for long-term comparative effectiveness and safety of diabetes medications

BMI = body mass index; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; RCT = randomized controlled trial.
*See text for more detail.

Conclusions

The evidence supports metformin as a firstline therapy, given its beneficial effects on HbA1c, weight, cardiovascular mortality (vs. sulfonylureas), and relative safety profile. The comparative long-term benefits and harms of other diabetes medications remain unclear. In this report, we provide comprehensive information comparing the benefits and common and serious harms of diabetes medications. In the absence of conclusive findings on long-term clinical and safety outcomes for most medication comparisons, this evidence synthesis can facilitate personalized treatment choices for clinicians and their patients, as well as support decisionmaking by payers and regulators.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014. www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf. Accessed February 26, 2015.
2. American Diabetes Association. Standards of medical care in diabetes-2014. Diabetes Care. 2014;37(Suppl 1):S14-S80. PMID: 24357209.
3. Qaseem A, Humphrey LL, Sweet DE, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31. PMID: 22312141.
4. American Diabetes Association. (7) Approaches to glycemic treatment. Diabetes Care. 2015 Jan;38 Suppl:S41-8. PMID: 25537707.
5. Garber A, Abrahamson M, Barzilay J, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement—executive summary. Endocr Pract. 2013;19(Suppl 2):1-48. PMID: 23816937.
6. Bolen S, Wilson L, Vassy J, et al. Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes. Comparative Effectiveness Review No 8. (Prepared by the Johns Hopkins Evidence-based Practice Center under Contract No. 290-02-0018.) AHRQ Publication No. 07-EHC010-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2007. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
7. Bennett WL, Wilson LM, Bolen S, et al. Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 27. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.) AHRQ Publication No. 11-EHC038-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
8. Colhoun HM, Livingstone SJ, Looker HC, et al. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012 Nov;55(11):2929-37. PMID: 22945303.
9. Lu CJ, Sun Y, Muo CH, et al. Risk of stroke with thiazolidinediones: a ten-year nationwide population-based cohort study. Cerebrovasc Dis. 2013;36(2):145-51. PMID: 24029780.
10. Mahaffey KW, Hafley G, Dickerson S, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J. 2013 Aug;166(2):240-9 e1. PMID: 23895806.
11. Mamtani R, Haynes K, Bilker WB, et al. Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. J Natl Cancer Inst. 2012 Sep 19;104(18):1411-21. PMID: 22878886.
12. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;17(1):1-12. PMID: 8721797.
13. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998 Jun;52(6):377-84. PMID: 9764259.
14. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60. PMID: 12958120.

15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID: 3802833.

16. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med. 2014 Feb 18;160(4):267-70. PMID: 24727843.

17. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.

18. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013 Aug 20;159(4):262-74. PMID: 24026259.

19. Shyangdan DS, Royle P, Clar C, et al. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev [serial on the Internet]. 2011;(10). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006423.pub2/abstract.

20. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013 May;36(5):1304-11. PMID: 23230096.

21. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006 Dec 7;355(23):2427-43. PMID: 17145742.

22. Ahren B, Johnson SL, Stewart M, et al. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care. 2014 Aug;37(8):2141-8. PMID: 24898304.

23. Schernthaner G, Duran-Garcia S, Hanefeld M, et al. Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). Diabetes Obes Metab. 2015 Jul;17(7):630-8. PMID: 25761977.

24. Schellhase KG, Koepsell TD, Weiss NS. Glycemic control and the risk of multiple microvascular diabetic complications. Fam Med. 2005 Feb;37(2):125-30. PMID: 15690253.

25. Vijan S, Hofer TP, Hayward RA. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. Ann Intern Med. 1997 Nov 1;127(9):788-95. PMID: 9382399.

26. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998 Sep 12;352(9131):837-53. PMID: 9742976.

27. Liu SC, Tu YK, Chien MN, et al. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. Diabetes Obes Metab. 2012 Sep;14(9):810-20. PMID: 22486990.

28. McIntosh B, Cameron C, Singh SR, et al. Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. Open Med. 2011;5(1):e35-48. PMID: 22046219.

29. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest. 2000 Aug;106(4):473-81. PMID: 10953022.

30. Purnell TS, Joy S, Little E, et al. Patient preferences for noninsulin diabetes medications: a systematic review. Diabetes Care. 2014 Jul;37(7):2055-62. PMID: 24963113.

31. Richter B, Bandeira-Echtler E, Bergerhoff K, et al. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev [serial on the Internet]. 2008;(2). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006739.pub2/abstract.

32. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 1991 Jun 26;265(24):3255-64. PMID: 2046107.

33. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ. 1998 Sep 12;317(7160):703-13. PMID: 9732337.

34. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ. 2000 Aug 12;321(7258):412-9. PMID: 10938049.

35. Wang JG, Staessen JA, Gong L, et al. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. Arch Intern Med. 2000 Jan 24;160(2):211-20. PMID: 10647760.

36. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001 Jan 4;344(1):3-10. PMID: 11136953.

37. Wu J, Kraja AT, Oberman A, et al. A summary of the effects of antihypertensive medications on measured blood pressure. Am J Hypertens. 2005 Jul;18(7):935-42. PMID: 16053990.

38. Nauman J, Janszky I, Vatten LJ, et al. Temporal changes in resting heart rate and deaths from ischemic heart disease. JAMA. 2011 Dec 21;306(23):2579-87. PMID: 22187277.

39. Singh N. Diabetes, heart rate, and mortality. J Cardiovasc Pharmacol Ther. 2002 Apr;7(2):117-29. PMID: 12075400.

40. Phung OJ, Schwartzman E, Allen RW, et al. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. Diabet Med. 2013 Oct;30(10):1160-71. PMID: 23663156.

41. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2013 Oct;15(10):938-53. PMID: 23594109.

42. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007 Jun 14;356(24):2457-71. PMID: 17517853.

43. U.S. Food and Drug Administration. FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines. 2013. www.fda.gov/downloads/Drugs/DrugSafety/UCM381108.pdf. Accessed February 25, 2015.

44. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26. PMID: 23992601.

45. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015 Jul 16;373(3):232-42. PMID: 26052984.

46. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet. 2015 May 23;385(9982):2067-76. PMID: 25765696.

47. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009 Jan 8;360(2):129-39. PMID: 19092145.

48. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010;340:b4909. PMID: 20061358.

49. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med. 2009 Oct 29;361(18):1736-47. PMID: 19850703.

50. Budnitz DS, Shehab N, Kegler SR, et al. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med. 2007 Dec 4;147(11):755-65. PMID: 18056659.

51. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007 Sep 29;370(9593):1129-36. PMID: 17905165.

52. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA. 2007 Sep 12;298(10):1189-95. PMID: 17848653.

53. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 Jun 5;373(9681):2125-35. PMID: 19501900.

54. GlaxoSmithKline. Highlights of Prescribing Information: Avandia (rosiglitazone maleate) tablets. 2014. http://us.gsk.com/products/assets/us_avandia.pdf. Accessed March 2, 2015.

55. Takeda Pharmaceuticals America. Highlights of Prescribing Information: Actos (pioglitazone) tables for oral use. 2013. http://general.takedapharm.com/content/file/pi.pdf?applicationcode=8a9c4571-a123-4477-91deb9cafe7d07e3&filetypecode=actospi. Accessed March 2, 2015.

56. U.S. Food and Drug Administration. FDA panel wants new DPP-4 inhibitor labels - cardiovascular data warrant new risk information for saxagliptin and alogliptin, advisers say. www.medpagetoday.com/PublicHealthPolicy/ClinicalTrials/50990. Accessed July 25, 2015.

57. Clinicaltrials.gov. CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes. 2010. https://clinicaltrials.gov/ct2/show/NCT01243424. Accessed July 30, 2015.

58. Clinicaltrials.gov. Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA). 2013. https://clinicaltrials.gov/ct2/show/NCT01897532. Accessed July 30, 2015.

59. U.S. Food and Drug Administration. Highlights of Prescribing Information: Victoza (liraglutide [rDNA origin] injection, solution for subcutaneous use. 2011. www.accessdata.fda.gov/drugsatfda_docs/label/2011/022341s004lbl.pdf. Accessed March 2, 2015.

60. U.S. Food and Drug Administration. Highlights of Prescribing Information: Tanzeum (albiglutide) for injection, for subcutaneous use. 2014. www.accessdata.fda.gov/drugsatfda_docs/label/2014/125431s000lbl.pdf. Accessed March 2, 2015.

61. U.S. Food and Drug Administration. Highlights of Prescribing Information: Bydureon (exenatide extended-release) for injectable suspension. 2015. www.fda.gov/safety/medwatch/safetyinformation/ucm400570.htm. Accessed August 7, 2015.

62. U.S. Food and Drug Administration. Trulicity (dulaglutide) injection, for subcutaneous use. 2015. www.fda.gov/safety/medwatch/safetyinformation/ucm442202.htm. Accessed August 7, 2015.

63. U.S. Food and Drug Administration. Incretin mimetic drugs for type 2 diabetes: early communication - reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas. 2013. www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm343805.htm. Accessed August 1, 2015.

64. Franciosi M, Lucisano G, Lapice E, et al. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One. 2013;8(8):e71583. PMID: 23936520.

65. Zhang ZJ, Bi Y, Li S, et al. Reduced risk of lung cancer with metformin therapy in diabetic patients: a systematic review and meta-analysis. Am J Epidemiol. 2014 Jul 1;180(1):11-4. PMID: 24920786.

66. Ferwana M, Firwana B, Hasan R, et al. Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies. Diabet Med. 2013 Sep;30(9):1026-32. PMID: 23350856.

67. Franks AS, Lee PH, George CM. Pancreatitis: a potential complication of liraglutide? Ann Pharmacother. 2012 Nov;46(11):1547-53. PMID: 23136352.

68. Kawalec P, Mikrut A, Lopuch S. The safety of dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose cotransporter 2 (SGLT-2) inhibitors added to metformin background therapy in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2014 May;30(4):269-83. PMID: 24829965.

69. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revised label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. 2015. www.fda.gov/Drugs/DrugSafety/ucm461449.htm. Accessed September 16, 2015.

70. U.S. Food and Drug Administration. Highlights of Prescribing Information. Invokana (canagliflozin) tablets, for oral use. 2015. www.accessdata.fda.gov/drugsatfda_docs/label/2015/204042s006lbl.pdf. Accessed September 16, 2015.

71. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. 2015. www.fda.gov/Drugs/DrugSafety/ucm446845.htm. Accessed July 25, 2015.

72. Erondu N, Desai M, Ways K, et al. Diabetic ketoacidosis and related events in the Canagliflozin Type 2 Diabetes Clinical Program. Diabetes Care. 2015 Sep;38(9):1680-6. PMID: 26203064.

73. Bristol-Myers Squibb. GLUCOPHAGE® (metformin hydrochloride) Tablets. GLUCOPHAGE® XR (metformin hydrochloride) Extended-Release Tablets. http://packageinserts.bms.com/pi/pi_glucophage_xr.pdf. Accessed July 30, 2015.

74. Bailey RA, Wang Y, Zhu V, et al. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: Improving Global Outcomes (KDIGO) staging. BMC Res Notes. 2014;7:415. PMID: 24990184.

75. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89. PMID: 16214598.

76. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009 Jan;32(1):84-90. PMID: 18931095.

77. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998 Sep 12;352(9131):854-65. PMID: 9742977.

78. Turner R, Murchison L, Wright AD, et al. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med. 1998;128(3):165-75. PMID: 9454524.

79. U.K. Prospective Diabetes Study. II. Reduction in HbA1c with basal insulin supplement, sulfonylurea, or biguanide therapy in maturity-onset diabetes. A multicenter study. Diabetes. 1985 Aug;34(8):793-8. PMID: 2862087.

80. United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ. 1995 Jan 14;310(6972):83-8. PMID: 7833731.

81. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2545-59. PMID: 18539917.

82. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2560-72. PMID: 18539916.

83. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA. 2008 Apr 2;299(13):1561-73. PMID: 18378631.

84. Wong HK, Ong KL, Cheung CL, et al. Utilization of glucose, blood pressure, and lipid lowering medications among people with type II diabetes in the United States, 1999-2010. Ann Epidemiol. 2014 Jul;24(7):516-21 e1. PMID: 24935464.

85. Patorno E, Patrick AR, Garry EM, et al. Observational studies of the association between glucose-lowering medications and cardiovascular outcomes: addressing methodological limitations. Diabetologia. 2014 Nov;57(11):2237-50. PMID: 25212258.

Introduction

Background

Type 2 diabetes currently affects 9.3 percent of the US population, or 29.1 million people.[1] The proportion of affected individuals in the US varies greatly by race and ethnicity: 16 percent of American Indian/ Alaska Natives, 13 percent of non-Hispanic black Americans and Hispanic Americans, 9 percent of Asian Americans, and 7 percent of non-Hispanic white Americans are afflicted with diabetes. The vast majority of these cases are type 2 diabetes.[2] Within these racial categories, rates also vary substantially within sub-populations (e.g., South Asian-Americans and East Asian-Americans).[2] Estimates of diabetes incidence that include laboratory-diagnosed diabetes, in addition to self-report, are higher than those reported by the US Centers for Disease Control and Prevention.[3] Encouragingly, most reports in the US and Europe suggest that the incidence of disease has *not* been rising over the past decade.[4] Similarly, the age at diagnosis has been relatively stable at 55 years in non-Hispanic whites, and 49 years in non-Hispanic blacks and Hispanics.[5]

Diabetes and its complications are a substantial public health burden, as they contribute significantly to mortality, morbidity, and health care costs.[1, 6] Costs related to diabetes were approximately $245 billion in 2012.[1] Complications of longstanding diabetes include the microvascular complications of retinopathy and blindness, neuropathy, nephropathy, and end-stage kidney disease. Diabetes is the most prevalent cause of new-onset blindness and new-onset end-stage renal disease in adults in the US. Diabetes also contributes importantly to macrovascular complications, including coronary artery disease, peripheral arterial disease, and carotid artery disease, and increases the risk of cardiovascular-related death nearly two-fold.[7]

Lifestyle modification and pharmacologic therapy are the cornerstones of the management of hyperglycemia for type 2 diabetes.[8] Results from randomized controlled trials have established that the risk of microvascular complications, particularly retinopathy, can be reduced with glycemic control in patients with type 2 diabetes.[9, 10] However, studies in the past decade have suggested that using diabetes medications to achieve *intensive* glycemic control [hemoglobin A1c (HbA1c) less than 7%] does not benefit cardiovascular morbidity and mortality[11, 12] and may harm patients, including those with important co-morbid conditions.[13] Recent work also suggests that the effects of intensive glucose lowering may vary across racial and ethnic groups.[14] These mixed results on the benefits and safety of glycemic control through pharmacologic therapy suggest the need for further research, including investigation of the long-term impact of glucose lowering therapies.

Even if questions about intensity of control are resolved, clinicians and other stakeholders need to determine the optimal agent for glucose lowering. Given the ever-increasing literature about type 2 diabetes medications and the recent approval of many new medications, an updated systematic review evaluating the effects of these medications on intermediate and long-term effectiveness and safety outcomes will be valuable to clinicians, patients, investigators, funders, guideline developers, and payers. In this era of intensive, direct-to-consumer marketing of new drugs, clinicians need a trustworthy source of comprehensive information about the comparative effectiveness and safety of medications. This review seeks to provide information about treatment options to a diverse set of clinicians, including family practitioners, general internists, nurse practitioners, physician assistants, nurses, pharmacists, endocrinologists, cardiologists, nephrologists, and others. Guideline developers may also find this review to be informative for clinical practice guideline preparation. Patients and patient advocates will find the information

valuable when making decisions about treatment options. Finally, investigators will be able to use the results of this review to identify gaps in the literature and formulate original research questions to fill these knowledge gaps.

Rationale for Update of Review on Comparative Effectiveness of Diabetes Medications

The Effective Health Care (EHC) Program of the Agency for Healthcare Research and Quality (AHRQ) has published two systematic reviews comparing monotherapies and medication combinations for adults with type 2 diabetes.[15, 16] In 2007, the AHRQ published its first systematic review, including 216 studies, on this topic.[15] This review concluded that most diabetes medications approved by the U.S. Food and Drug Administration (FDA) had similar effects on reducing HbA1c, and most drugs, except for metformin and acarbose, caused at least modest increases in body weight. The sulfonylurea class was associated with an increased risk of hypoglycemia, metformin with gastrointestinal problems, and the thiazolidinediones with heart failure. Importantly, the literature was too sparse to support any conclusions about differential effects of the oral diabetes medications on all-cause mortality, cardiovascular mortality and morbidity, and microvascular complications. When asked by AHRQ to update that review in 2011, we identified an additional 140 randomized controlled trials and 26 observational studies.[16] We found that most medications lowered HbA1c by 1 absolute percentage point, on average, but metformin was more effective for HbA1c-lowering than the dipeptidyl-peptidase 4 (DPP-4) inhibitors, a newer class of diabetes medications approved since the initial report. Mostly, the two-drug combinations had similar effects on HbA1c reduction. Compared with metformin, thiazolidinediones and sulfonylureas contributed to more weight gain. Sulfonylureas had a four-fold higher risk of mild/moderate hypoglycemia compared with metformin alone, and, in combination with metformin, had more than a five-fold increased risk of hypoglycemia when compared with metformin plus thiazolidinediones. The risk of congestive heart failure was higher with thiazolidinediones than with sulfonylureas, and the risk of bone fractures was higher with thiazolidinediones than with metformin. Thus, the evidence continued to support use of metformin as a first line agent, based on its effects on HbA1c and weight and side effect profile. The risk of adverse effects was the main determinant of the risk-benefit balance for the two-drug combinations.

Despite the addition of important evidence on the HbA1c-lowering and adverse effects of the FDA-approved diabetes medications in 2011, data on the then recently-approved medication classes (glucagon-like peptide-1 (GLP-1) agonists and DPP-4 inhibitors) were sparse, and data on long-term outcomes for both older and newer medications were still lacking.[17, 18] Based on these prior systematic reviews, metformin has strong evidence to support its use as an initial pharmacologic treatment for most patients with type 2 diabetes;[7] It's use as a first-line therapy has been widely promoted by clinical practice guidelines.[19-21] Not all patients, however, can successfully use metformin due to contraindications to its use or intolerance of its side effects. The evidence base regarding alternative monotherapies for these patients continues to evolve.

Since January 2010, one new medication class [the sodium-glucose cotransporter 2 (SGLT-2) inhibitors, with three new medications] and several new DPP-4 inhibitors and GLP-1 receptor agonists have been approved by the FDA. Also since 2010, additional data on previously-approved medications have emerged that could change the balance of benefit and risk attributable to these drugs or could alter the strength of evidence about some of the drug comparisons previously reviewed.[22-25] Including insulin, there are 10 medication classes with

approval by the FDA for treatment of type 2 diabetes. We limited the add-on insulins to premixed or basal insulins in the 2011 report since these are often used as a second line agent after metformin. We have included most, although not all medication classes, in this updated systematic review (Table 1).

Table 1. Characteristics of medications included in this report

Class	Main Mechanism of Action	Drug	Trade Name	Dosing
Biguanides	Inhibit glucose production by the liver	Metformin	Glucophage®, Glucophage XR®	Oral: 500 to 2550 mg divided doses (qd to tid) Max dose: 2550 mg; 2000 mg for XR
Thiazolidinediones	Increase glucose uptake by skeletal muscle	Pioglitazone	Actos®	Oral: 15 to 30 mg qd Max dose: 45 mg qd
		Rosiglitazone	Avandia®	Oral: 4 to 8 mg qd or 2 to 4 mg bid Max dose: 8 mg qd or 4 mg qd with insulin or sulfonylurea
Sulfonylureas	Increase insulin secretion by pancreatic beta cells	Glimepiride	Amaryl®	Oral: 1 to 8 mg qd Max dose: 8 mg qd
		Glipizide	Glucotrol®, Glucotrol XL®	Oral: 5 to 15 mg qd or 5 to 20 mg bid Max dose: 20 mg bid, 20 mg qd for XL
		Glyburide or glibenclamide	DiaBeta®, Glynase® PresTab®, Micronase®	Oral: 2.5 to 20 mg qd or bid Max dose: 20 mg qd
DPP-4 inhibitors	Increase incretin hormone activity which increases insulin release and decreases inappropriate glucagon production by the pancreatic islet cells*	Alogliptin	Nesina®	Oral: 6.25 to 25 mg qd Recommended dose: 25 mg qd
		Linagliptin	Tradjenta®	Oral: 5 mg qd Recommended dose: 5 mg qd
		Saxagliptin	Onglyza®	Oral: 2.5 to 5 mg qd Recommended dose: 2.5 or 5 mg qd
		Sitagliptin	Januvia®	Oral: 25 to 100 mg qd Recommended dose: 100 mg qd
SGLT-2 inhibitors	Increases urinary excretion of glucose	Canagliflozin	Invokana®	Oral: 100 to 300 mg Max dose: 300 mg
		Dapagliflozin	Farxiga®	Oral: 5 to 10 mg qd Max dose: 10 mg qd
		Empagliflozin	Jardiance®	Oral: 10 to 25 mg qd Max dose: 25 mg qd

Table 1. Characteristics of medications included in this report (continued)

Class	Main Mechanism of Action	Drug	Trade Name	Dosing
GLP-1 receptor agonists	Increase glucose-dependent insulin release and decrease inappropriate glucagon production by the pancreatic islet cells*	Albiglutide injection	Tanzeum®	SC injection: 30 mg qw Max dose: 50 mg qw
		Dulaglutide injection	Trulicity®	SC injection: 0.75 to 1.5 mg/0.5 mL Max dose: 1.5 mg/0.5 mL
		Exenatide injection	Byetta®	SC injection: 5 to 10 mcg SC bid
		Liraglutide injection	Victoza®	SC injection: 1.6 to 1.8 mg SC qd
Basal insulin	Increases long-acting insulin	NPH insulin	Humulin N®, Novolin N®	NA
		Insulin detemir	Levemir®	NA
		Insulin glargine	Lantus®	NA
Premixed insulin	Increases short and long-acting insulin	50% NPH and 50% regular insulin	Humulin® 50/50	NA
		70% NPH and 30% regular insulin	Humulin® 70/30 Novolin® 70/30	NA
		50% lispro protamine suspension and 50% lispro	Humalog Mix® 50/50	NA
		75% lispro protamine suspension and 25% lispro	Humalog Mix® 75/25	NA
		70% aspart protamine suspension and 30% aspart	NovoLog Mix® 70/30	NA

bid = twice daily; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; mcg = microgram; mg = milligrams; mL = milliliter; NA = not applicable since there is no maximum dose for these insulins; NPH = neutral protamine Hagedorn; qd = once daily; qw = once weekly; SC = subcutaneous; SGLT-2 = sodium-glucose co-transporter-2; tid = three-times daily; XL = extended release; XR = extended release.

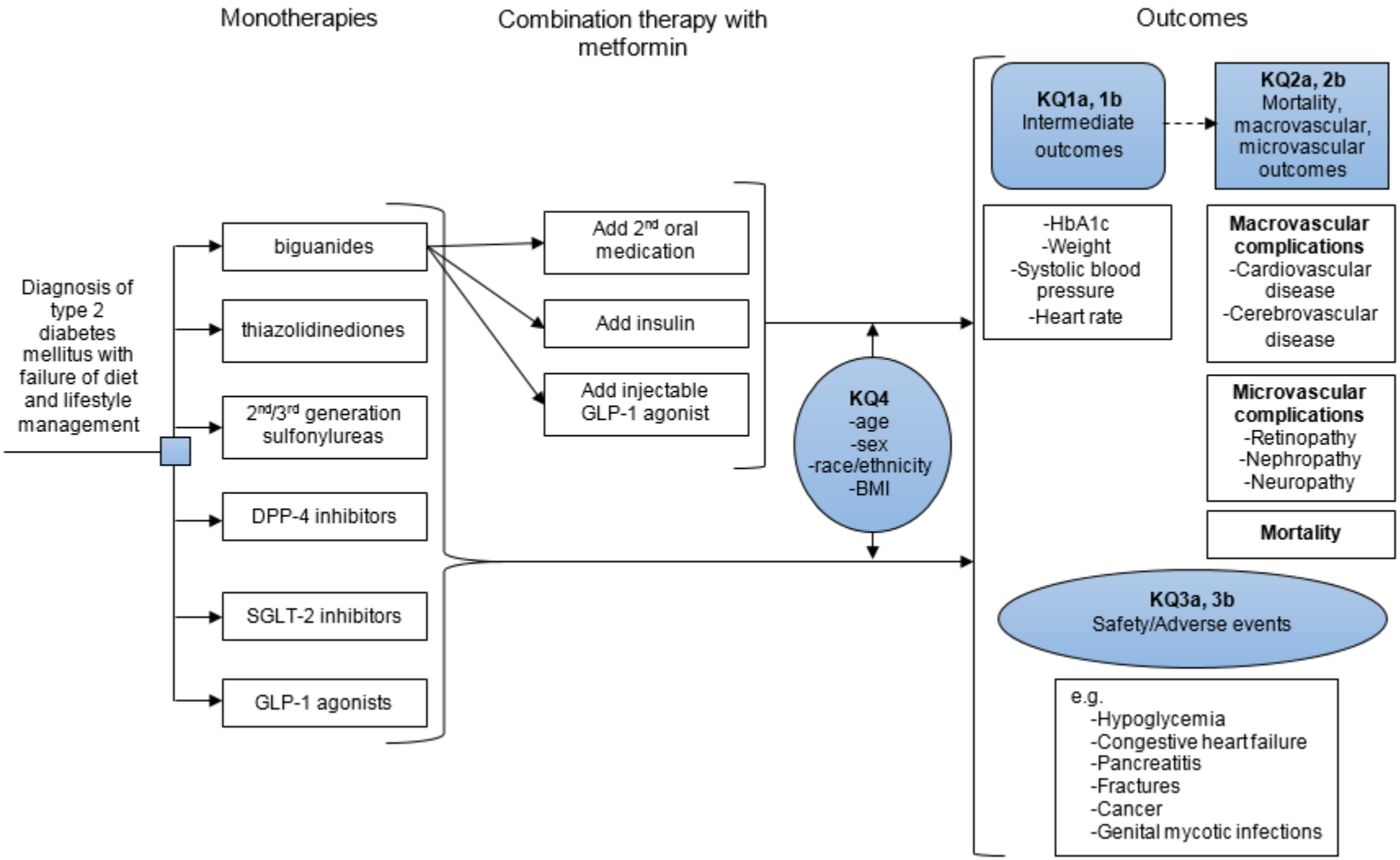
* Decreased glucagon production decreases glucose production by the liver.

Analytic Framework

Our analytic framework describes the decisions that patients and their providers face when managing type 2 diabetes pharmacologically (Figure 1). It highlights the comparisons and outcomes of interest that correspond to each of the Key Questions in our review. When beginning medical treatment, patients usually start with one of five drug classes (Table 1), which have all been FDA-approved for monotherapy. These include biguanides, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists. Clinical guidelines of the American Diabetes Association recommend monitoring HbA1c to determine the need for changing the medication dose or adding another agent to improve glycemic control.[26] If the HbA1c is not adequately controlled, clinicians typically add an additional oral

diabetes medication, or they may add insulin or a noninsulin injectable medication like a GLP-1 receptor agonist. Clinicians also monitor other intermediate outcomes, such as weight and short-term and long-term safety and adverse effects of the drugs, which vary by drug class. The ultimate goal is to improve long-term outcomes while maximizing quality of life.

Figure 1. Analytic framework



BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; GLP1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; KQ=Key Question; NPH = neutral protamine Hagedorn; SGLT-2 inhibitor = sodium-glucose co-transporter 2

Scope

This review updates the 2011 review on oral diabetes medications for adults with type 2 diabetes.[16] In this review, we have chosen to focus on head-to-head drug class comparisons for which there are evidence gaps (see Table 2). We have included a new FDA-approved class of oral diabetes medications, the SGLT-2 inhibitors, including empagliflozin, dapagliflozin, and canagliflozin. We have included new DPP-4 inhibitors approved since the last review, linagliptin and alogliptin, and GLP-1 receptor agonists approved since the last review, albiglutide and dulaglutide. After discussion with our technical expert panel, we excluded head-to-head intraclass drug comparisons and excluded placebo-controlled trials since these comparisons were considered lower priority given the large number of head-to-head studies. Since most guidelines recommend metformin as first-line therapy,[19-21] we have chosen to focus Key Questions 1b, 2b, and 3b on metformin-based combination comparisons to assess second-line therapy options after metformin.

Given the unique and emerging safety concerns of some of these medications, we have included additional safety outcomes in the review, including impaired renal function, urinary tract infections, genital infections, volume depletion, and bone fractures for studies that include a comparison with SGLT-2 inhibitors. We have also included systolic blood pressure and heart rate as intermediate outcomes for studies including either SGLT-2 inhibitors or GLP-1 receptor agonists.

We have chosen to exclude meglitinides as interventions of interest as they are uncommonly used in current clinical practice (<1% of hypoglycemic prescriptions).[27, 28] We evaluated meglitinides in our two earlier systematic reviews and found that this class has similar effects on HbA1c and similar rates of hypoglycemia as sulfonylureas. The 2011 update included little new information on meglitinides, and we expected to find little additional evidence for this class of medication.

Similarly, we are no longer reporting on lipid levels as intermediate outcomes of interest. LDL targets are no longer universally the primary factor guiding the use of cholesterol-lowering therapy. Current guidelines suggest that 10-year global cardiovascular disease (CVD) risk should be used to determine statin usage and intensity, and this global risk score does not actually include low-density lipoprotein cholesterol.[29] Furthermore, triglycerides and high-density lipoprotein are not usual targets of cholesterol therapy. Statin usage is recommended for all patients 40 years of age and older with diabetes in the US.[30] Based on these new approaches to lipids, we did not feel that evidence of the impact of diabetes medications on lipid levels would be substantially informative to clinical care to warrant inclusion in this report.

Key Questions

Key Question 1a: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified monotherapy FDA-approved diabetes medications (see Table 2) for the intermediate outcomes of hemoglobin A1c, weight, systolic blood pressure (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists), and heart rate (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists)?

Key Question 1b: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified metformin-based combinations of FDA-approved diabetes medications (see Table 2) for the intermediate outcomes of hemoglobin A1c, weight,

systolic blood pressure (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists), and heart rate (for comparisons including SGLT-2 inhibitors or GLP-1 receptor agonists)?

Key Question 2a: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified monotherapy FDA-approved diabetes medications (see Table 2) for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

Key Question 2b: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified metformin-based combinations of FDA-approved diabetes medications (see Table 2) for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

Key Question 3a: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the specified monotherapy FDA-approved diabetes medications (see Table 2) regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; and for comparisons including SGLT-2 inhibitors, urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

Key Question 3b: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the specified metformin-based combinations of FDA-approved diabetes medications (see Table 2) regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; and for comparisons including SGLT-2 inhibitors, urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

Key Question 4: Do the comparative safety and effectiveness of these treatments differ across subgroups defined by the age, sex, race/ethnicity, and body mass index (BMI) of adults with type 2 diabetes?

Table 2. Priority medication comparisons included for each Key Question

Intervention	Main Intervention Class (Generic Individual Drug Names)	Comparisons
Monotherapy as main intervention	Biguanides (metformin)	• Thiazolidinediones* • Sulfonylureas† • DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 receptor agonists‡ • Combination of metformin plus thiazolidinedione • Combination of metformin plus sulfonylurea • Combination of metformin plus DPP-4 inhibitor • Combination of metformin plus SGLT-2 inhibitor • Combination of metformin plus GLP-1 receptor agonist
	Thiazolidinediones (rosiglitazone, or pioglitazone)	• Sulfonylureas • DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 receptor agonists
	Sulfonylureas (glimepiride, glyburide¶, glibenclamide¶, or glipizide)	• DPP-4 inhibitors • SGLT-2 inhibitors • GLP-1 receptor agonists
	DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, or sitagliptin)	• SGLT-2 inhibitors • GLP-1 receptor agonists
	SGLT-2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin)	• GLP-1 receptor agonists
Combination therapy as main intervention	Combination of metformin plus (thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT-2 inhibitor or GLP-1 receptor agonist or basal insulin)	• Combination of metformin plus (sulfonylurea or DPP-4 inhibitor or SGLT-2 inhibitor or GLP-1 receptor agonist or basal insulin‡ or premixed insulin‡)

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; SGLT-2 = sodium-glucose co-transporter 2

* For studies comparing thiazolidinediones with metformin, we reviewed only HbA1c, long-term outcomes, and selected safety outcomes given the **high strength of evidence** from our prior Comparative Effectiveness Review for other outcomes (specifically fracture and weight).[16]

† For studies comparing sulfonylureas with metformin, we reviewed only the long-term outcomes and cancer given the **high strength of evidence** on the other outcomes from our prior Comparative Effectiveness Review.[16]

‡ The generic individual drug names for the GLP-1 receptor agonists are exenatide, liraglutide, dulaglutide, and albiglutide. The generic individual drug names for basal insulin are insulin glargine, insulin detemir, and neutral protamine Hagedorn (NPH) insulin. The generic individual drug names for premixed insulin are NPH/regular 50/50, NPH/regular 70/30, insulin lispro 50/50, insulin lispro 75/25, and insulin aspart 70/30.

¶ Glyburide and glibenclamide are the same drug.

Methods

Topic Refinement and Review Protocol

This review updates the 2011 review on oral diabetes medications for adults with type 2 diabetes.[16] We recruited a Technical Expert Panel (TEP) to review a draft of the protocol and a summary of the revisions from the 2011 review (see the Scope and Key Questions section from the Introduction). The TEP included endocrinologists, general internists, biostatisticians, and representatives from government agencies. The TEP reviewed our protocol and provided feedback on the proposed methods for addressing the Key Questions. With the feedback from the TEP and the Agency for Healthcare Research and Quality (AHRQ) representatives, we finalized the protocol and posted it on AHRQ Effective Health Care Program's Web site (www.effectivehealthcare.ahrq.gov).

Literature Search Strategy

Search Strategy

The 2011 review searched the following databases for the dates listed: MEDLINE® (1966 to April 2010), Embase® (1974 to April 2010), and the Cochrane Central Register of Controlled Trials (CENTRAL). Per AHRQ's guidance, our new search dates overlapped the prior search by more than 1 year.[31] We ran the search developed for the 2011 review with the date restrictions of April 2009 through April 2015 (see Appendix A).

An additional expanded search included medical subject headings (MeSH) and text words for all of the new medications included in this updated report. The expanded search did not have any date restrictions.

We handsearched the reference lists of all newly included articles and relevant systematic reviews. Additionally, we searched ClinicalTrials.gov to identify relevant registered trials. We also reviewed the Web site of the Food and Drug Administration (FDA) for any unpublished additional studies relevant to the topic as part of our grey literature search. We also provided an opportunity for manufacturers of interventions to submit unpublished data.

Study Selection

All of the review authors participated in the study selection. Two independent reviewers conducted title scans. For a title to be eliminated at this level, both reviewers needed to indicate that the study was ineligible. If the reviewers disagreed, the article was advanced to the next level, which was abstract review.

The abstract review phase was designed to identify studies reporting the effectiveness or safety of the medications and medication combinations of interest. Abstracts were reviewed independently by two investigators and were excluded if both investigators agreed that the article met one or more of the exclusion criteria (see the inclusion and exclusion criteria listed in Table 3). Differences between investigators regarding the inclusion or exclusion of abstracts were tracked and resolved through consensus adjudication.

Articles promoted on the basis of the abstract review underwent another independent parallel review to determine if they should be included in the final qualitative and quantitative systematic

review and meta-analysis. The differences regarding article inclusion were tracked and resolved through consensus adjudication.

Table 3. Inclusion and exclusion criteria

PICOTS	Inclusion Criteria	Exclusion Criteria
Population	• We included studies of adult humans with type 2 diabetes, non-insulin dependent diabetes mellitus, or adult-onset diabetes.	• We excluded studies of patients with type 1 diabetes, impaired glucose tolerance, metabolic syndrome, maturity onset diabetes of youth, and gestational diabetes. • We excluded studies if they included only pregnant women or subjects 17 years of age or younger. • We excluded studies where everyone was required to have at least one of the following comorbid conditions: ESLD, ESRD, cancer, new onset diabetes after organ transplant, or a recent cardiovascular event within the 3 months prior to study start.
Interventions	• We included studies that evaluated a diabetes medication of interest or drug combination of interest (see Table 2).	• We excluded studies that did not specify the adjunctive medications, such as those stating use of "any oral hypoglycemic," or if the study listed several possible medications without stratification of the results by treatment.
Comparisons	• We included studies that evaluated a comparison of interest (see Table 2).	• We excluded studies that did not have a comparison group or that used a placebo comparison or non-pharmacological comparison. • We excluded intraclass head-to-head comparisons.

Table 3. Inclusion and exclusion criteria (continued)

PICOTS	Inclusion Criteria	Exclusion Criteria
Outcomes*	• We included studies addressing the following intermediate outcomes for KQ1: ▪ Hemoglobin A1c^ ▪ Weight† ▪ Systolic blood pressure‡ ▪ Heart rate‡ • We included studies addressing the following microvascular, macrovascular, and mortality outcomes for KQ2: ▪ All-cause mortality ▪ Cardiovascular and cerebrovascular morbidity and mortality ▪ Retinopathy ▪ Nephropathy ▪ Neuropathy • We included studies addressing the following safety outcomes for KQ3: ▪ Liver injury^ ▪ Impaired renal function§ ▪ Lactic acidosis^ ▪ Pancreatitis^ ▪ Hypoglycemia^ ▪ Gastrointestinal side effects^ ▪ Congestive heart failure^ ▪ Cancer ▪ Macular edema or decreased vision^ ▪ Fractures§ ▪ Urinary tract infections§ ▪ Genital mycotic infections§ ▪ Volume depletion§ • KQ4 included studies considering any of the above outcomes.	
Type of study	• For KQ1, we included only RCTs. • For KQ2 and KQ3, we included RCTs, non-randomized experimental studies with a comparison group, and high-quality observational studies with a comparison group. • We included randomized trials utilizing a crossover design with some exceptions.‖	• We excluded studies not written in English¶ and excluded articles with no original data. • We excluded meeting abstracts.
Timing and setting		• We excluded studies in which the observed intervention or exposure period was less than 3 months, 12 weeks, or 90 days.

ESLD = end-stage liver disease; ESRD = end-stage renal disease; KQ = Key Question; PICOTS = populations, interventions, comparisons, outcomes, timing, and settings; RCT = randomized controlled trial

***** Of note, some outcomes could be classified as either safety or long-term clinical outcomes (e.g., myocardial infarction and cancer).

^ We did not evaluate this outcome for metformin vs. sulfonylurea comparisons as the evidence was high from the prior report.

† We did not evaluate this outcome for metformin vs. thiazolidinedione or metformin vs. sulfonylurea comparisons as the evidence was high from the prior report.

‡ We evaluated this outcome only for comparisons that included a GLP-1 receptor agonist or a SGLT-2 inhibitor.

§ We evaluated this outcome only for comparisons that included a SGLT-2 inhibitor.

‖ For crossover randomized trials, we abstracted data on all outcomes at the end of the first period prior to the crossover. If data were not presented at the end of the first period, then we excluded the article for the following outcomes where we would be

unable to draw conclusions about causality: long-term outcomes (KQ2), fractures, cancer, intermediate outcomes in studies where there was a washout period of less than 3 months; and safety outcomes in studies where the washout period was less than a month except for hypoglycemia, gastrointestinal side effects, and liver injury.

¶ We decided to include non-English language articles through the full text article review phase of the updated search and assess the volume and content of these articles along with workload to determine if abstracting data from these articles would add value to the review.

Data Extraction

We used a systematic approach to extract all data to minimize the risk of bias in this process. We used standardized forms from the previous reviews as templates for data extraction and pilot tested them for the new medications and outcomes (Appendix B). By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

We double-reviewed all data abstracted from the studies. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. A third reviewer audited a random sample of articles to ensure consistency in the data abstraction of the articles. Reviewers were not masked to the authors of the articles, their respective institutions, nor the journals in which their articles were published.

For all articles, the reviewers extracted information on the general study characteristics (e.g., study design, study period, and followup); study participants (e.g., age, sex, race, weight/body mass index [BMI], hemoglobin A1c levels, and duration of diabetes); interventions (e.g., initial, maximum, and mean doses, frequency of use, duration of use, and permissibility of treatment intensification with additional therapies), comparisons; the method of ascertainment of safety outcomes; and the outcome results, including measures of variability. We also collected data on outcomes for the subgroups of interest: age, sex, race/ethnicity, and BMI.

For continuous outcomes, we extracted the mean difference between groups and a measure of dispersion. If the between-group difference was not reported, we calculated the point estimate of the difference using the mean difference from baseline for each group. If the mean difference from baseline was not reported, we calculated this from the baseline and final values for each group.[32] If there were no measures of dispersion for the mean difference from baseline for each group, we calculated the variance using the standard deviation of the baseline and final values, assuming a correlation between baseline and final values of 0.5.

We entered all information from the article review process into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada). Reviewers entered comments into the system whenever applicable. The DistillerSR database was used to maintain the data and to create detailed evidence tables and summary tables. Data will later be uploaded into the Systematic Review Data Repository.

Risk of Bias Assessment of Individual Studies

Two independent reviewers assessed study quality. We assessed the risk of bias in individual randomized controlled trials (RCTs) using the Jadad criteria consistent with the prior report.[33] Although newer quality assessment tools exist, we felt that continuing to use the Jadad criteria would be adequate and consistent with our previous methods. We used the Downs and Black tool for assessment of risk of bias for non-randomized trials and observational studies.[34] Given that observational studies with a high risk of bias add little value to a systematic review of effectiveness,[35] we included only medium- and high-quality observational studies as determined

by assessment of each study's risk of bias. For inclusion, we required that observational studies account for the following potential confounders: age, sex, either race or socioeconomic status, and co-morbid conditions (quantified with a co-morbidity scale or index, or by inclusion of other medical conditions or medications used by the patient, or with valid methods to adjust for confounding by indication or restricted to one race or age group making adjustment unnecessary). If the study met the confounding criteria, the observational study was considered eligible for inclusion in the review. We also applied the Downs and Black tool and other inclusion criteria for nonrandomized trials and observational studies to the non-randomized trials and observational studies that had been included in the prior report.[16]

Data Synthesis

For each Key Question, we created a set of detailed evidence tables containing all information extracted from eligible studies, including those from the prior evidence reports. We included both the results of individual studies included in the prior report and the results of newly-identified studies. We conducted meta-analyses when there were sufficient data (at least three trials) and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and drug dose). For trials having more than one dosing arm, we chose the arm for inclusion that had dosing most consistent with the other trials considered for inclusion in the meta-analysis. When more than one followup interval was reported, we used the data from the followup most similar to the other trials. While there is no definitive cut-point for long-term versus short-term, we considered trials lasting 2 years or longer to be "long-term" since a multifactorial intervention in adults with type 2 diabetes has shown changes in morbidity starting as early as 2 years.[36]

We tested the heterogeneity among the trials considered for quantitative pooling using a standard chi-squared test using a significance level of alpha less than or equal to 0.10. We also examined heterogeneity among studies with an I-squared statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance. We considered a value greater than 50 percent to indicate substantial heterogeneity.[37] We pooled the mean difference between groups using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity (I-squared <50%).[38] We pooled studies using the profile likelihood estimate when we detected high statistical heterogeneity (I-squared >50%).[39] When data were insufficient or inappropriate to combine in a meta-analysis, we summarized the outcomes by reporting the ranges of values for mean differences from baseline or mean differences between groups, when available.

Since we anticipated that most drugs would have similar physiologic effects within a class, we combined studies of unique medications within classes when reporting outcomes *except* where known differences exist (e.g., the effects of pioglitazone and rosiglitazone on cardiovascular outcomes). If we saw substantial heterogeneity (I-squared >50%) in pooled estimates for any outcome, we stratified studies by medication within a class and repeated the pooled analyses and recalculated measures of heterogeneity. Additionally, when there were at least 10 studies for a given comparison and outcome and evidence of statistical heterogeneity, we attempted to determine other reasons for heterogeneity by evaluating study-level characteristics, such as baseline values of the outcome, study duration, quality measures, or dosing differences between study arms using metaregression techniques. We also conducted sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimates.

For the outcome of hypoglycemia, we conducted separate analyses for: (a) severe hypoglycemia and (b) mild or moderate or total hypoglycemia. The categories were based on the definitions of hypoglycemia provided in the studies. For hypoglycemia and all other dichotomous outcomes, we calculated pooled odds ratios using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity[38] or the profile likelihood estimate in settings of high heterogeneity.[39]

Reporting Bias Assessment

We assessed reporting biases in the included RCTs as follows:[40]

1. Publication bias was evaluated by:
    a. Using the Begg and Mazumdar[41] and the Egger[42] test to quantitatively assess for publication bias when there were at least 10 studies for a given comparison and outcome pair
    b. Comparing ClinicalTrials.gov entries and actual publications for evidence of absence of published literature
    c. Comparing FDA medical and statistical reviews and actual publications for evidence of absence of published literature (results are detailed in Appendix E).

2. Selective Outcomes Reporting bias was evaluated by comparing differences in reporting on the outcomes of hemoglobin A1c (HbA1c), hypoglycemia, and all-cause mortality in the actual publications to the FDA medical and statistical reviews.

3. Selective Analysis Reporting bias was evaluated by assessing the precision of outcome data reporting by determining the number of studies which reported on an outcome of interest (e.g., HbA1c) but did not report a measure of dispersion completely or at all. We assessed this for the outcomes of HbA1c, hypoglycemia, and all-cause mortality. For dichotomous outcomes (hypoglycemia and all-cause mortality), we evaluated the number of studies reporting the n of events uniformly across all arms. We reviewed this for the studies included for the update only.

Strength of the Body of Evidence

At the completion of our review, two reviewers sequentially graded the available evidence addressing the Key Questions by adapting an evidence grading scheme recommended by the Guide for Conducting Comparative Effectiveness Reviews.[43] We applied evidence grades to the bodies of evidence about each intervention comparison for each outcome that were addressed by at least one RCT or three observational studies. We separately assessed the strength of evidence for shorter and longer studies (2 years or greater); however, we only assessed strength of evidence for longer studies where we could draw a conclusion. We assessed the study limitations, consistency, directness, precision, and reporting bias.

We assessed the study limitations of individual studies using the tools described in the Risk of Bias of Individual Studies section. We started with the assumption that randomized controlled trials would have "low" study limitations and observational studies would have "medium" study limitations. We downgraded the study limitations score based on the items in the quality assessment tools.

We rated the body of evidence as "consistent" if most of the studies (about 75%) showed the same direction of effect. We rated the consistency of comparison-outcome dyads for which there was only a single study as "unknown." All other bodies of evidence were rated as "inconsistent."

We rated the bodies of evidence for all outcomes as "direct," except for heart rate and liver injury. We rated the bodies of evidence for heart rate as "indirect," because the association between heart rate and clinically important outcomes such as mortality is less strong in adults with diabetes.[44] We rated the bodies of evidence for the outcome of liver injury as "indirect," since most of the studies used liver injury enzyme elevation as the indicator of injury.

If we conducted a meta-analysis for a body of evidence, we relied on the results of the meta-analysis to rate precision and used the designated minimally important differences as a point of reference for precision. For continuous outcomes, we rated the body of evidence as "imprecise" if one-half of the width of the confidence interval for the meta-analysis was wider than the minimally important difference. We defined the minimally important difference to be 0.3% for HbA1c, 1 kg for weight, and 3 mmHg for systolic blood pressure. While there are no strict definitions of what should be considered clinically relevant differences, we used minimally important differences that clinical experts suggested are clinically relevant and that are supported, in part, in the literature.[45] If there was no meta-analysis, we rated precision by evaluating the narrowness of the confidence intervals or the magnitude of the *P*-value. For dichotomous outcomes, we evaluated precision using the optimal information size for that outcome. If the total sample size across both arms of the studies was greater than the optimal information size, then we rated the body of evidence as "precise." Otherwise, it was rated as "imprecise." We estimated rough optimal information sizes using the Mantel Hanszel model for relative odds and incorporating the approximate baseline rate of the outcome and the desired minimum detectable relative odds (Table 4).[46]

Table 4. Optimal information size for one arm and classification of dichotomous outcomes for optimal information size

	"Low" Detectable OR, 1.05	"Medium" Detectable OR, 1.5	"High" Detectable OR, 2.0
"Low" baseline risk, 0.01	654,548 (All-cause mortality, cardiovascular mortality, cardiovascular morbidity, cancer, diabetic nephropathy)	8,364 (Liver injury, pancreatitis, severe allergic reaction, renal impairment, congestive heart failure, microalbuminuria, volume depletion)	2,597
"Medium" baseline risk, 0.15	51,168 (Severe hypoglycemia)	690 (Urinary tract infections, genital infections)	225
"High" baseline risk, 0.3	31,296	446 (Hypoglycemia)	153 (Gastrointestinal events)

OR = odds ratio

We rated reporting bias by evaluating publication bias, selective outcomes reporting bias, and selective analysis reporting bias (described in the Reporting Bias Assessment section). If any of these domains was rated as "suspected," then we rated the body of evidence as having "suspected" reporting bias. Otherwise, we rated reporting bias as "undetected."

We classified evidence pertaining to the Key Questions into four categories: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect but further research could change

our confidence in the estimate of the effect and may change the estimate); (3) "low" grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) "insufficient" grade (indicating evidence is unavailable or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion). We provided a conclusion regarding whether a given drug was favored over another (or if neither was favored) when the evidence permitted this. For all-cause mortality, cardiovascular mortality, cardiovascular morbidity, and safety outcomes, if we concluded that neither arm was favored (i.e., benefit or harm excluded), we did not rate the evidence as "moderate" in strength if the evidence was underpowered (rated as "imprecise").

We graded the evidence separately for the RCTs and the observational studies.[43] The final evidence grade and conclusion was typically based on the RCT grade and could be strengthened by evidence from the observational studies. We noted differences between RCT and observational evidence in the text, when present.

Applicability

We discussed the applicability of studies in terms of the degree to which the study population (e.g., age, sex, race/ethnicity, and co-morbid conditions), interventions (e.g., dose, frequency, rescue therapy, and duration of exposure), outcomes (e.g., outcome definition and reporting), and settings are typical of the treatment of individuals with type 2 diabetes who are receiving treatment in a usual care setting (conceived as outpatient treatment by internists, family physicians, and endocrinologists).

Peer Review and Public Commentary

Experts in endocrinologists, general internists, epidemiologists, biostatisticians, and representatives from government agencies were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in a disposition of comments report that will be made available 3 months after the Agency posts the final systematic review on the EHC Web site.

Results

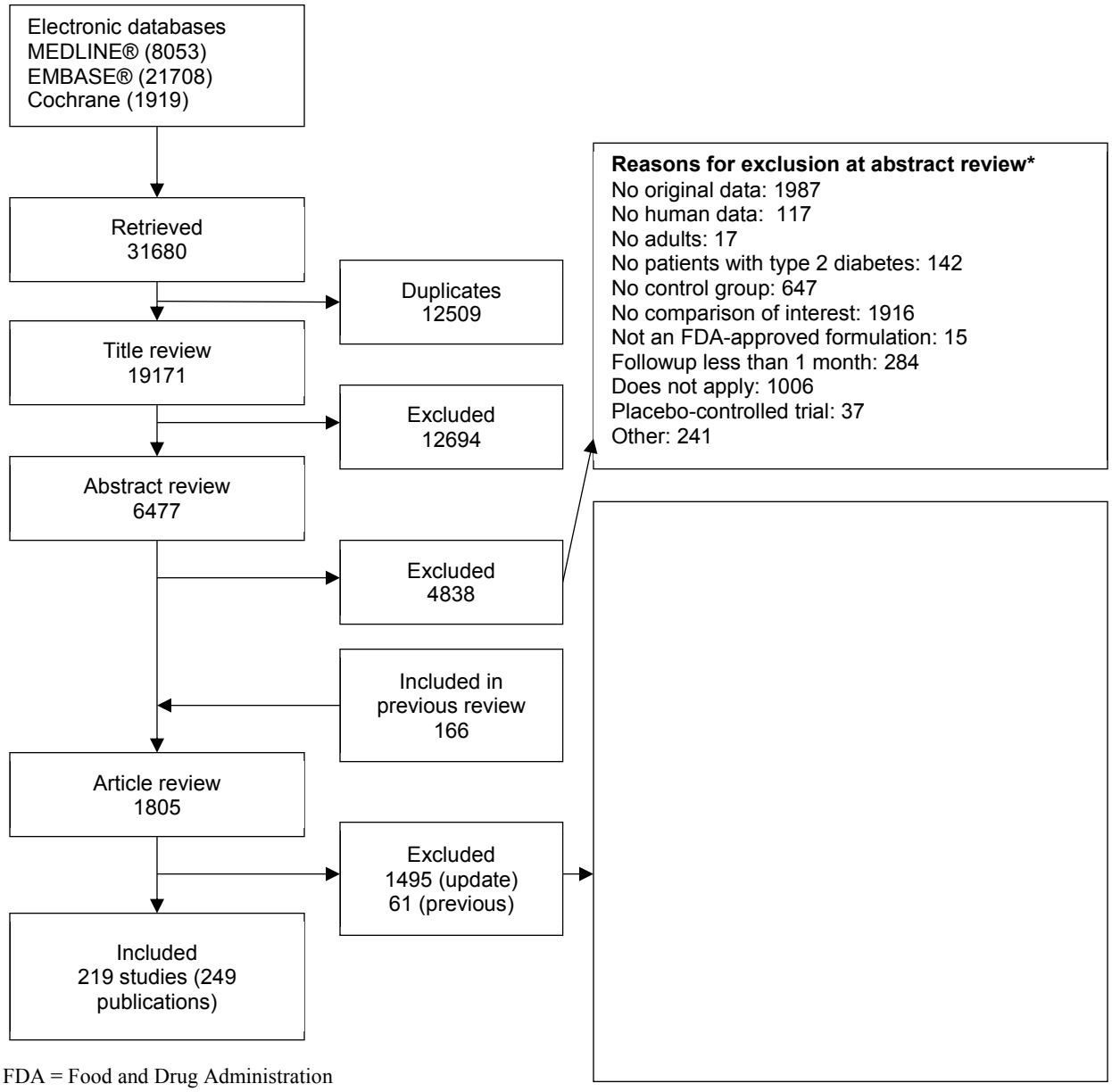
Results of Literature Searches

We included 166 publications in our previous review. After excluding studies without a comparison or an outcome relevant to this update, and cohort studies not meeting our revised quality criteria, we included 105 studies (published in 107 articles) in this update.

We retrieved 19,171 unique citations from our updated literature search (Figure 2). After reviewing titles, abstracts, and full text, we included 114 new studies (published in 142 new articles). Ten of the new publications were either extensions or additional analyses of studies included in the previous review.

In total, we include in this review 219 studies, published in 249 articles.

Figure 2. Summary of the search (number of articles)

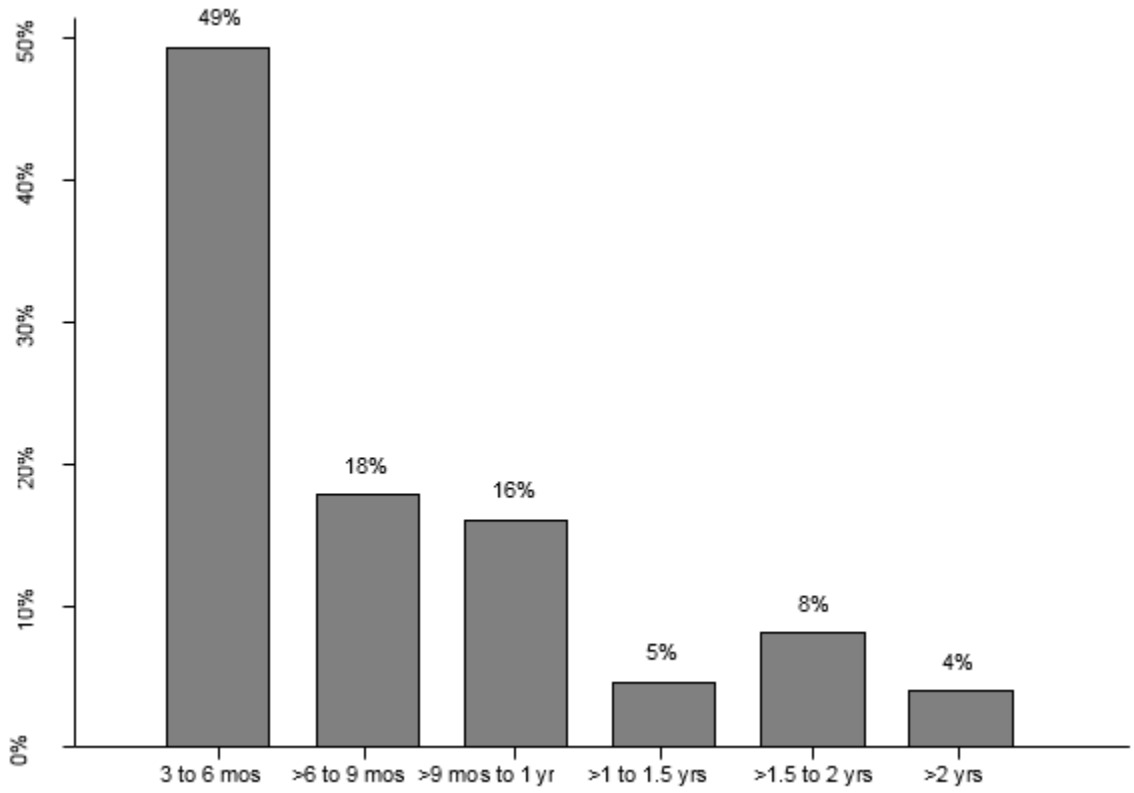


FDA = Food and Drug Administration
* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.
† Comorbid condition restrictions were end-stage renal disease, end-stage liver disease, cancer, new onset diabetes after transplant, or a cardiovascular event within 3 months (e.g., acute coronary syndrome, acute myocardial infarction, post-coronary artery bypass graft surgery, or with drug-eluting stents)

Study Duration of RCTs for All Key Questions (KQ1–KQ4)

Of the 177 included randomized controlled trials (RCTs) for all Key Questions combined, most studies were less than a year (Figure 3). Only 4 percent of studies lasted over 2 years, making it difficult to draw any firm conclusions about long-term outcomes. Unless stated otherwise in the text or figures below, results and conclusions for all the Key Questions are for short-term outcomes.

Figure 3. Duration of followup for randomized controlled trials comparing the effects of diabetes medications among adults with type 2 diabetes (N = 177)



Key Questions 1a and 1b: Intermediate Outcomes

Study Design and Population Characteristics

One hundred sixty-two RCTs (reported in 189 articles) evaluated intermediate clinical outcomes for adults with type 2 diabetes and met our inclusion criteria (Appendix D, Tables D1 to D4). All trials were parallel arm RCTs, except one which also used a crossover design[47] and one which also used a factorial design.[48] About half of the trials answering Key Question 1 occurred partly or exclusively in the United States (US) (n = 26), Japan (n=13), Italy (n = 12), and/or were multi-national (n = 56); the rest of the trials occurred in developed or newly industrialized countries. These RCTs lasted from 12 weeks to 5.5 years; however, most studies (81%) lasted less than 1 year, and only six studies lasted more than 2 years (including the well-known Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD), and A Diabetes Outcome Progression Trial (ADOPT)).[49-54] Only 12 percent of studies (n=20) reported receiving no pharmaceutical support, while about 14 percent of RCTs (n = 22) did not describe whether or not they received pharmaceutical support. The number of studies not describing their pharmaceutical support dropped from 25 percent of the studies included in the last diabetes medication comparative effectiveness report[16] to only 5 percent of the newly included 87 studies in this update. The use of rescue therapy (i.e., the addition of another diabetes medication when the blood sugar was not controlled on the randomized treatment regimen) was not reported in 41 of the 87 studies included (47.1%), was not allowed in

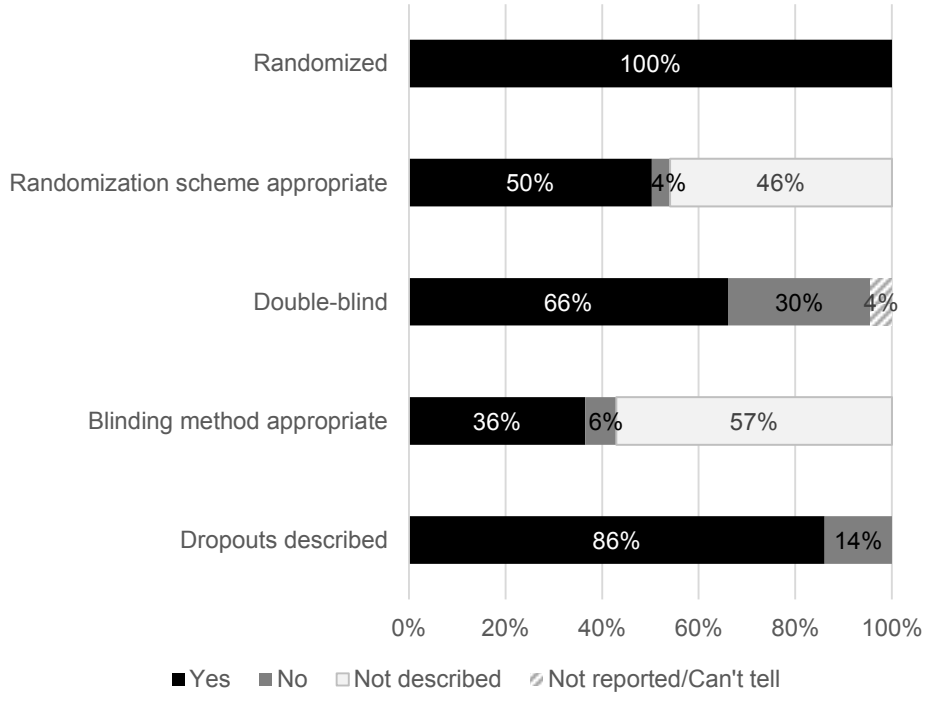
20 studies (23.0%), and was allowed in 26 studies (29.9%). In the studies where rescue therapy was allowed, 12 studies did not specify which medications were used and, when reported, the medications varied greatly.

Study participants were mainly middle-aged, overweight, or obese adults who had had diabetes for 3 to 7 years. The exclusion criteria were generally similar for most trials: significant renal, cardiovascular, and hepatic disease. About half of the trials (58%) excluded older subjects (generally over the age of 75 to 80). Almost all of the studies included men and women. About 28% of the RCTs did not report race/ethnicity. In this update, the percent not reporting race/ethnicity increased from 20% of the 119 studies in the prior report[16] to 38% of the 89 studies in the newly included studies. In these studies, when race was reported, most subjects were Caucasian, but between 10% and 20% of the enrolled population was of other races. The mean baseline HbA1c among study subjects varied from 6 to 12 absolute percentage points, with most subjects having a mean baseline HbA1c between 7 and 9 absolute percentage points.

Risk of Bias

All of the studies included in this section were described as randomized (Figure 4). Fifty percent described their randomization scheme; 66 percent described their study as double-blinded. About one-third (36%) of all double-blinded RCTs also described the steps taken to ensure blinding. The majority of trials (86%) described the withdrawals and dropouts. Twelve of the fifteen studies with at least 2 years of followup had over 20% losses to followup.

Figure 4. Summary of the risk of bias of randomized controlled trials evaluating intermediate outcomes



Key Points and Evidence Grades for Intermediate Outcomes

Hemoglobin A1c

Monotherapy Comparisons

- Most oral diabetes medications had similar efficacy in achieving reductions in hemoglobin A1c (HbA1c).
  - In the prior report, the strength of evidence was graded as high that metformin was similar to sulfonylurea (pooled between-group difference of 0.1%; 95% confidence interval [CI], -0.1% to 0.3%). Therefore, we did not update this comparison for HbA1c in this review.
  - The strength of evidence (SOE) was graded as high that metformin was similar to thiazolidinedione (pooled between-group difference of -0.04%; 95% CI, -0.11% to 0.03%).
  - Thiazolidinediones performed similarly to sulfonylureas (pooled between-group difference of -0.04%; 95% CI, -0.13% to 0.06%). (SOE: High)
  - The SOE was graded as low or insufficient for all the monotherapy comparisons of the newer classes of sodium-glucose cotransporter (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, and will warrant further study.
- The one exception was that metformin had a greater reduction in HbA1c compared with dipeptidyl peptidase-4 (DPP-4) inhibitors (pooled between-group difference of -0.4%; 95% CI, -0.5% to -0.3%). (SOE: High)

Metformin-Based Combination Comparisons

- The combination of metformin plus GLP-1 receptor agonists reduced HbA1c more than metformin plus DPP-4 inhibitors, with a pooled between-group difference of -0.65% (95% CI, -0.75% to -0.54%) in the short-term. (SOE: Moderate)
- Most other combination therapy comparisons had either no significant or no clinically meaningful (<0.3%) between-group differences in HbA1c between arms.
- The evidence was graded as moderate for the following comparisons: metformin plus a thiazolidinedione versus metformin plus a sulfonylurea, metformin plus a thiazolidinedione versus metformin plus a DPP-4 inhibitor, metformin plus a sulfonylurea versus metformin plus an SGLT-2 inhibitor, metformin plus a DPP-4 inhibitor versus metformin plus an SGLT-2 inhibitor, and metformin plus a DPP-4 inhibitor versus metformin plus a GLP-1 receptor agonist.
- Despite the clinical interest in comparing metformin plus injectables, there was insufficient or low strength of evidence on glycemic control for the following comparisons: metformin plus the GLP-1 receptor agonists versus metformin plus basal or premixed insulin, and metformin plus premixed insulin versus metformin plus basal insulin.

Weight

Monotherapy Comparisons

- In the 2011 report, metformin had greater weight reduction than thiazolidinediones (pooled mean between-group difference of -2.6 kg; 95% CI, -4.1 kg to -1.2 kg) or

sulfonylureas (pooled mean between-group difference of -2.7 kg; 95% CI, -3.5 kg to -1.9 kg) with high strength of evidence. Therefore, we did not update these two comparisons in this report.

- Metformin had greater weight reduction than DPP-4 inhibitors (pooled mean between-group difference, -1.3 kg; 95% CI, -1.6 kg to -1.0 kg). (SOE: High)
- SGLT-2 inhibitors had greater weight reduction when compared with metformin or DPP-4 inhibitors (between-group differences ranging from -1.3 kg to -2.7 kg). (SOE: Moderate for both comparisons)
- DPP-4 inhibitors and GLP-1 receptor agonists both decreased weight more than thiazolidinediones (between-group differences ranging from -2.3 kg to -3.5 kg). (SOE: Moderate for both comparisons)
- GLP-1 receptor agonists decreased weight more than sulfonylureas (pooled mean between-group difference, -2.3 kg; 95% CI, -3.3 kg to -1.2 kg). (SOE: Moderate)
- Sulfonylureas caused slightly less weight gain when compared with thiazolidinediones (between-group difference of -1.2 kg; 95% CI, -1.8 kg to -0.6 kg). (SOE: Moderate)

Metformin Versus Metformin-Based Combination Comparisons

- Metformin monotherapy reduced weight more than the combination of metformin plus a thiazolidinedione (pooled mean between-group difference, -2.2 kg; 95% CI, -2.6 kg to -1.9 kg) or metformin plus a sulfonylurea (pooled mean between-group difference, -2.2 kg, 95% CI, -3.4 kg to -1.0 kg). (SOE: High for both comparisons)
- When compared with metformin monotherapy, the combination of metformin plus
  - SGLT-2 inhibitor had greater weight reduction (pooled mean between-group difference, -2.0 kg; 95% CI, -2.5 kg to -1.5 kg). (SOE: High)
  - GLP-1 receptor agonist had greater weight reduction (pooled mean between-group difference, -2.0 kg; 95% CI, -2.7 kg to -1.3 kg). (SOE: Moderate)
- Metformin monotherapy had no significant differences in weight when compared with the combination of metformin plus DPP-4 inhibitors (pooled mean between-group difference, -0.1 kg; 95% CI, -0.2 kg to 0.03 kg). (SOE: Moderate)

Metformin-Based Combination Comparisons

- The combinations of metformin plus a sulfonylurea, metformin plus a GLP-1 receptor agonist, and metformin plus a DPP-4 inhibitor all had a more favorable effect on weight compared with metformin plus a thiazolidinedione (range in between-group differences, -0.9 kg to -5.1 kg). (SOE: Moderate for all comparisons)
- When compared with the combination of metformin plus a sulfonylurea, the combination of metformin plus
  - DPP-4 inhibitors had more favorable effects on weight (pooled mean between-group difference, -2.2 kg; 95% CI, -1.8 kg to -2.5 kg). (SOE: High)
  - SGLT-2 inhibitors had more favorable effects on weight (pooled mean between-group difference, -4.7 kg; 95% CI, -4.4 kg to -5.0 kg). (SOE: High)
  - GLP-1 receptor agonist had more favorable effects on weight (range in mean between-group differences, -2.4 kg to -12.3 kg). (SOE: Moderate)
  - Premixed insulin or basal insulin had less favorable effects on weight (range in mean between-group differences, 0.5 kg to 1.7 kg). The strength of evidence was low for both comparisons, due to the small number of studies. However, taken together, the

strength of evidence would be moderate favoring metformin plus sulfonylurea over metformin plus a premixed or long-acting insulin.

- When compared with metformin plus a DPP-4 inhibitor, the combination of metformin plus
  - GLP-1 receptor agonist had greater reductions in weight (pooled mean between-group difference, -1.8 kg; 95% CI, -1.1 kg to -2.5 kg). (SOE: Moderate)
  - SGLT-2 inhibitors had greater reductions in weight (between-group differences of around -2.5 kg). (SOE: Moderate)
- Despite the clinical interest in comparing metformin plus injectables, there was low strength of evidence on weight for the following comparisons: metformin plus the GLP-1 receptor agonists versus metformin plus basal or premixed insulin, and metformin plus premixed insulin versus metformin plus basal insulin.

Systolic Blood Pressure (for Comparisons That Include SGLT-2 Inhibitors or GLP-1 Receptor Agonists)

Monotherapy Comparisons

- SGLT-2 inhibitors had a greater reduction in systolic blood pressure compared with metformin, (pooled between-group difference of -2.8 mmHg; 95% CI, -2.6 mmHg to -3.0 mmHg). (SOE: Moderate)
- The strength of evidence was graded low or insufficient for the following comparisons:
  - SGLT-2 inhibitors versus DPP-4 inhibitors, and
  - GLP-1 receptor agonists versus metformin, thiazolidinediones, sulfonylureas, and DPP-4 inhibitors.

Metformin Versus Metformin-Based Combination Comparisons

- Metformin plus a SGLT-2 inhibitor reduced systolic blood pressure more than metformin alone (pooled between-group difference of -4.4 mmHg; 95% CI, -2.9 to -6.0 mmHg) for shorter studies. (SOE: High)
- Metformin plus a GLP-1 receptor agonist reduced systolic blood pressure more than metformin alone (pooled between-group difference of -3.1 mmHg; 95% CI, -1.4 to -4.9 mmHg). (SOE: Moderate)

Metformin-Based Combination Comparisons

- Metformin plus a SGLT-2 inhibitor reduced systolic blood pressure more than metformin plus a sulfonylurea (pooled between-group difference, -5.0 mmHg; 95% CI, -4.2 mmHg to -6.0 mmHg) or metformin plus a DPP-4 inhibitor (pooled between-group difference, -4.1 mmHg; 95% CI, -3.6 mmHg to -4.6 mmHg). (SOE: High and Moderate, respectively)

Heart Rate (for Comparisons That Include SGLT-2 Inhibitors or GLP-1 Receptor Agonists)

Monotherapy Comparisons

- Metformin compared with a GLP-1 receptor agonist yielded no differences in heart rate between arms. (SOE: Moderate)

Metformin Versus Metformin-Based Combination Comparisons

- There was low or insufficient evidence for all metformin combination therapies compared with metformin alone.

Metformin-Based Combination Comparisons

- Combination therapy with metformin plus a SGLT-2 inhibitor resulted in less increase in heart rate compared with metformin plus a sulfonylurea (pooled between group difference in heart rate, -1.5 bpm; 95% CI, -0.6 bpm to -2.3 bpm). (SOE: Moderate)

Evidence for Hemoglobin A1c

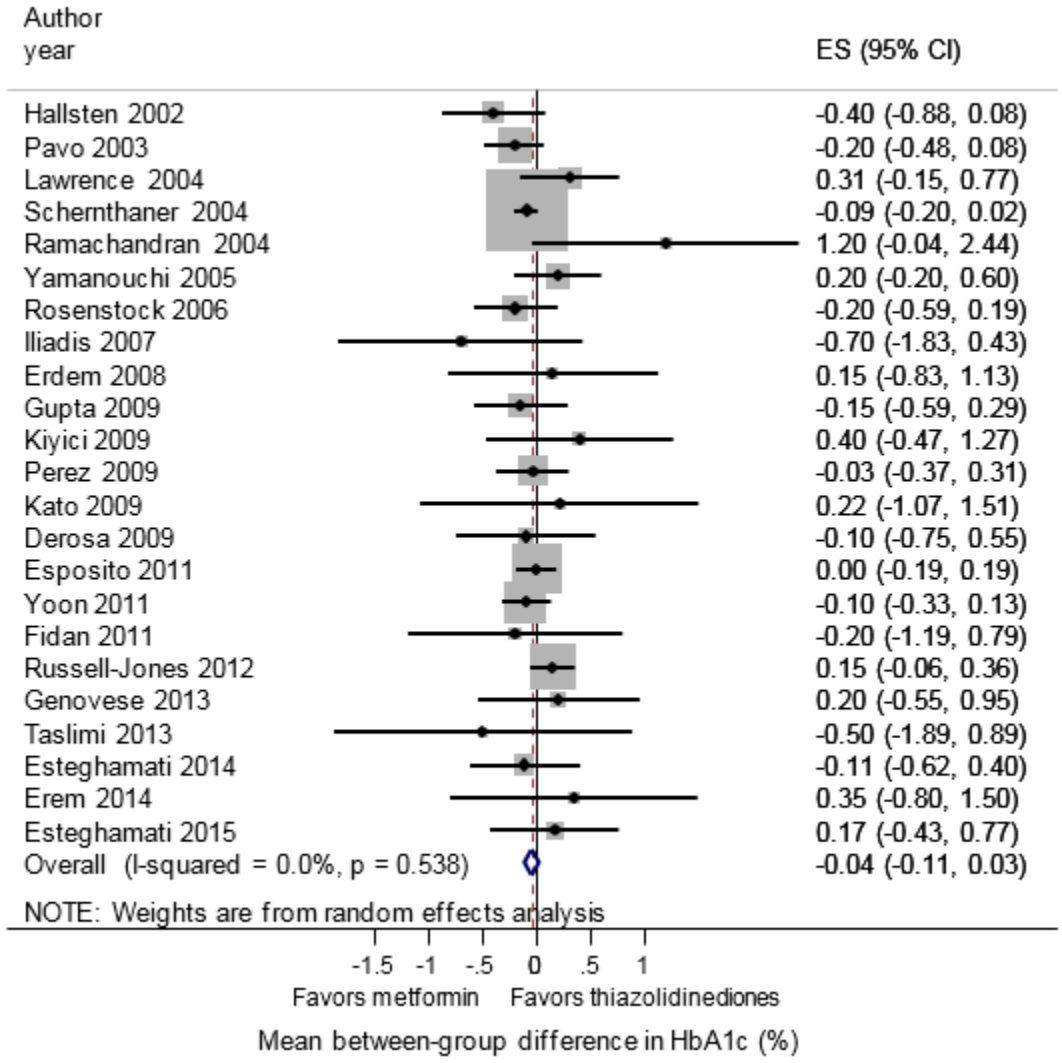
Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Twenty-three RCTs, each lasting approximately one year or less, directly compared metformin with a thiazolidinedione, and showed no between-group differences in HbA1c (pooled between-group difference of -0.04%; 95% CI, -0.11% to 0.03%) (Figure 5).[55-77] We tested the effect of each individual study on the combined point estimate. No single study influenced the pooled results. No substantial heterogeneity was identified.

Three additional trials examined this comparison but were excluded from the pooled results, one with a median study duration of 4 years,[50] one which reported median HbA1c instead of means,[78] and one study where the mean difference between groups could not be calculated.[79] The 4-year, double-blind RCT (known as the ADOPT study), with around a 60% loss to followup, was designed to compare long-term glycemic control between metformin, rosiglitazone, and glyburide monotherapy as initial treatment for adults with type 2 diabetes.[50] The authors found a statistically significant but small difference between groups favoring rosiglitazone (mean difference between groups 0.1%; 95% CI, 0.05% to 0.2%). Of note, the HbA1c decreased in all groups for the first 6 months and then increased in all groups over the rest of the study. The other two short duration RCTs excluded from the meta-analysis were consistent with the pooled results. One study reported no between-group differences in median HbA1c.[78] The second study was missing the number in each arm needed to calculate the between-group difference. Since this was an RCT, we calculated the between-group difference with the assumption of equal numbers in each arm which showed no statistically significant differences between-groups in HbA1c.[79] (SOE: High; Neither drug favored)

Figure 5. Pooled mean between-group difference in hemoglobin A1c comparing metformin with thiazolidinediones



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus Sulfonylureas

In the prior report, we graded the evidence as high showing no differences in HbA1c between groups for this comparison. Therefore, we did not re-evaluate this comparison for HbA1c.

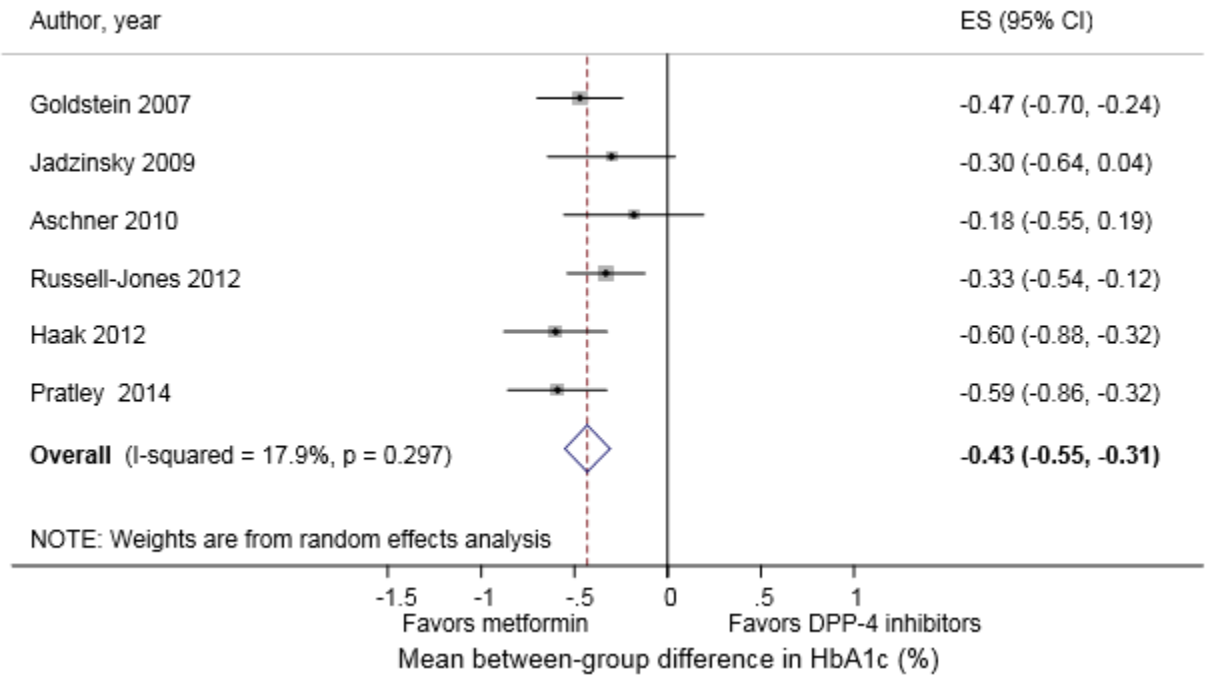
Metformin Versus DPP-4 Inhibitors

Six short duration RCTs (reported in nine articles) compared metformin with DPP-4 inhibitors (sitagliptin, alogliptin, linagliptin and saxagliptin).[73, 80-87] These studies reported greater reductions in HbA1c with metformin (pooled between-group difference in HbA1c of -0.4%; 95% CI, -0.5% to -0.3%) (Figure 6). No single study strongly influenced the meta-analysis results. In the three studies using both low and high metformin dosages compared with the

maximum dose DPP-4 inhibitor, we included the maximum dose metformin arm in the meta-analysis to make the drug dosages most comparable. The lower dose metformin arms (1000 mg) compared with maximum dose DPP-4 showed no statistically significant between-group differences in HbA1c.[84-86]

Two RCTs (in five articles) were reported as extension studies.[80, 81, 83, 85, 87] The shorter duration results were included in the meta-analysis, since their study durations were more similar to the other studies in the meta-analysis. The first RCT comparing metformin 1000 mg twice daily with sitagliptin 100 mg daily reported HbA1c at 24 weeks,[80] 54 weeks,[81] and 104 weeks.[85] The between-group difference in HbA1c of -0.5 percent favored metformin over sitagliptin at both 24 and 54 weeks of followup. At week 104, there was no significant difference between groups in HbA1c, but there were high and differential losses to followup among the arms (74% loss to followup in the sitagliptin arm and 48% in the metformin arm). The second 76-week study[87] was an RCT initially reported at 24 weeks comparing metformin up to 1000 mg twice daily with saxagliptin 10 mg daily. In this study, the between-group difference of -0.3 in HbA1c non-significantly favored metformin at 24 weeks[83] and statistically significantly favored metformin at 76 weeks (mean difference between-groups in HbA1c, -0.2%; 95% CI, -0.5% to -0.03%),[87] which is consistent with the meta-analysis results. (SOE: High; Metformin favored)

Figure 6. Pooled mean between-group difference in hemoglobin A1c comparing metformin with DPP-4 inhibitors



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus SGLT-2 Inhibitors

Three short duration and one longer duration RCTs (reported in three articles) compared metformin with an SGLT-2 inhibitor, showing no consistent between-group differences in

HbA1c among the studies.[88-90] We did not combine these studies in a meta-analysis due to dosing and study duration differences. Two of the short duration studies reported in one article compared metformin XR titrated to 2000 mg with dapagliflozin 5 mg in the first study, and compared metformin XR titrated to 2000 mg with dapagliflozin 10 mg in the second study.[88] Both studies, each lasting 24 weeks, reported no significant between-group differences in HbA1c.[88] The study comparing metformin XR to the lower dose dapagliflozin arm of 5 mg had a mean difference between-groups in HbA1c which favored metformin by 0.16 percent although non-significantly, and the study comparing metformin XR to the higher dose dapagliflozin arm of 10 mg did not favor either arm. The third study comparing a lower dose of metformin XR of 1500 mg daily with dapagliflozin 10 mg daily for 12 weeks favored the dapagliflozin arm (calculated mean between-group difference in HbA1c of 0.12%; 95% CI, 0.08% to 0.16%).[89] The 90-week RCT comparing metformin 1000 mg twice daily with empagliflozin 10 mg daily and 25 mg daily reported no significant differences between groups in HbA1c.[90] (SOE: Low; Neither drug favored)

Metformin Versus GLP-1 Receptor Agonists

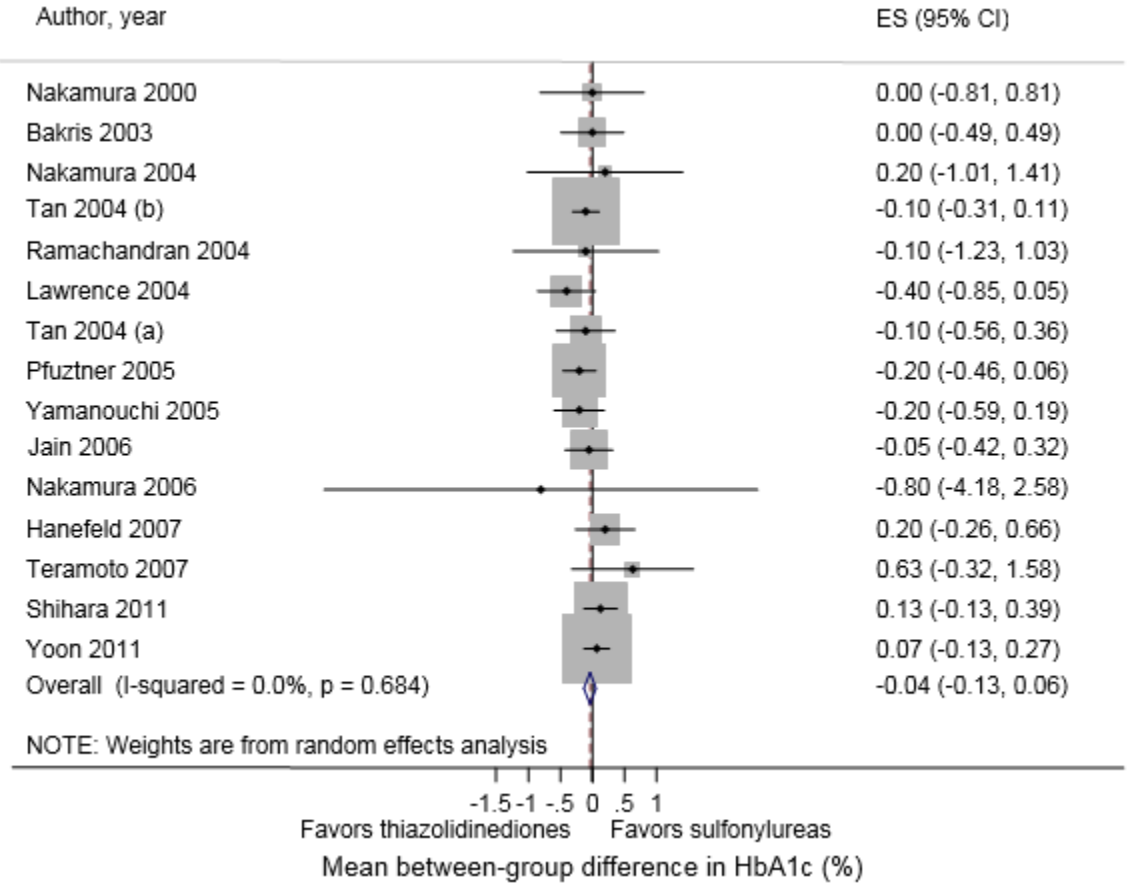
Three studies, each lasting one year or less, compared metformin versus a GLP-1 receptor agonist, with no consistent between-group differences in HbA1c.[73, 91, 92] We did not combine the studies in a meta-analysis due to study duration and dosing differences. Each study, lasting 24 to 52 weeks in duration, compared metformin at 1500 mg or higher to a GLP-1 receptor agonist (exenatide twice daily in one study, exenatide weekly in a second study, and dulaglutide weekly in a third study). Only one study had a borderline significant result, favoring dulaglutide 1.5 mg weekly over metformin titrated to 2000 mg daily after 52 weeks (calculated mean between-group difference in HbA1c of 0.2%; 95% CI, 0.0% to 0.4%).[91] This same study also had a lower-dose dulaglutide arm at 0.75 mg weekly, which showed no significant difference in HbA1c when compared with metformin titrated to 2000 mg daily.[91] (SOE: Low; Neither drug favored)

Thiazolidinediones Versus Sulfonylureas

Thiazolidinediones (pioglitazone and rosiglitazone) and sulfonylureas (glibenclamide, glimepiride, and glyburide) had similar effects on HbA1c in 15 short duration RCTs (pooled mean between-group difference of -0.04%; 95% CI, -0.13% to 0.06%) (Figure 7).[60, 61, 63, 74, 93-103] In a sensitivity analysis, we found no single study influenced the results , and there was no substantial heterogeneity between studies. We excluded one short duration RCT from the meta-analysis, since it did not report a number for analysis in each arm.[79] This open-label 12-week RCT compared rosiglitazone titrated to 4-8 mg daily with glipizide titrated to 5-15 mg daily and reported a greater reduction in HbA1c in the thiazolidinedione arm (-0.9%) compared with the glipizide arm (-0.3%).[79]

We excluded the ADOPT study from the meta-analysis due to its long duration (median followup of 4 years).[50] As mentioned previously, this double-blind RCT evaluated the long-term glycemic control between metformin, rosiglitazone, and glyburide monotherapy as initial treatment for type 2 diabetic adults, and had a 62 percent, 63 percent, and 56 percent loss to followup, respectively, in each treatment arm. The between-group difference between rosiglitazone and glyburide favored rosiglitazone after 4 years (mean difference between-groups of -0.4%; 95% CI, -0.5% to -0.3%). Of note, glyburide reduced HbA1c more than rosiglitazone, initially. HbA1c then rose higher in the glyburide arm than in the rosiglitazone arm after 1.5 years. (SOE: High; Neither drug favored in the short-term. SOE: Insufficient for the long-term.)

Figure 7. Pooled mean between-group difference in hemoglobin A1c comparing thiazolidinediones with sulfonylureas



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Thiazolidinediones Versus DPP-4 Inhibitors

Three RCTs, each lasting less than 26 weeks, compared pioglitazone with the DPP-4 inhibitors alogliptin and sitagliptin with no clear between-group differences in HbA1c (range in between-group differences of -0.48% to 0.23%).[48, 73, 104] We did not combine the studies due to dosing differences among the studies. The one RCT with maximal dosing in both arms (pioglitazone titrated to 45 mg daily in one arm and sitagliptin 100 mg daily in the other arm) favored pioglitazone over sitagliptin (between-group difference in HbA1c of -0.5%; 95% CI -0.7% to -0.3%).[73] The other two RCTs used maximum dose DPP-4 inhibitors compared with moderately-dosed pioglitazone at 30 mg daily and reported no significant between-group differences in HbA1c.[48, 104] (SOE: Insufficient)

Thiazolidinediones Versus GLP-1 Receptor Agonists

Two comparably-dosed RCTs compared pioglitazone with exenatide in differing dosing regimens, with mixed results.[73, 105] One double-blind, moderately-sized RCT compared pioglitazone titrated to 45 mg daily with exenatide 2 mg weekly.[73] After 26 weeks, the mean

between-group difference in HbA1c was -0.1% with a reported 98.3% CI of -0.15% to 0.35%.[73] The second open-label RCT compared pioglitazone at 45 mg daily with exenatide 10 ug twice daily. After 48 weeks, the calculated mean between-group difference in HbA1c favored exenatide by 0.3% (95% CI, 0.0% to 0.6%).[105] (SOE: Insufficient)

Sulfonylureas Versus DPP-4 Inhibitors

Three RCTs, each lasting 54 weeks or less, compared a sulfonylurea (glipizide or glimepiride) with a DPP-4 inhibitor (sitagliptin or linagliptin) with no clear between-group differences in HbA1c.[106-108] We did not combine these studies in a meta-analysis due to dosing differences and study population differences. Two RCTs non-significantly favored sulfonylureas over the DPP-4 inhibitor arms (between-group differences in HbA1c of -0.22% and -0.28%).[106, 108] The third RCT enrolled patients with moderate or severe renal insufficiency at baseline and compared glipizide (mean dose 7.7 mg) with sitagliptin at 25 or 50 mg daily, depending on the participant's renal function.[107] This study showed no significant between-group differences in HbA1c.[107] (SOE: Insufficient)

Sulfonylureas Versus GLP-1 Receptor Agonists

Four RCTs (reported in five articles) compared sulfonylureas directly with a GLP-1 receptor agonist (all studies using liraglutide).[109-113] Three of the four studies favored liraglutide over sulfonylureas.[109, 110, 112, 113] We did not combine these trials in a meta-analysis due to dosing differences between studies. Only two of the four studies used comparable dosing in the two arms. The first reported no statistically significant differences between the two arms.[111] The second RCT favored the GLP-1 arm (between-group difference in HbA1c of 0.6%; 95% CI, 0.4% to 0.8%, at 52 weeks, and 0.3%; 95% CI, 0.2% to 0.4%, at the 104-week followup).[112, 113] The two other RCTs, lasting 24 and 52 weeks, significantly favored the liraglutide arm by 0.5% each;[109, 110] yet both of these studies used relatively lower doses in the sulfonylurea arm compared with the liraglutide arm, making it difficult to discern drug differences versus dosing differences.[109, 110] (SOE: Insufficient)

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

Only one double-blind, moderately-sized RCT, lasting 24 weeks, compared the DPP-4 inhibitor sitagliptin at 100 mg daily with the SGLT-2 inhibitor empagliflozin at 10 mg and 25 mg daily.[114] The lower dose empagliflozin arm showed no significant between-group differences in HbA1c when compared with sitagliptin 100 mg daily. The higher dose empagliflozin 25 mg arm was favored slightly, but not significantly, over sitagliptin 100 mg (between-group difference in HbA1c of 0.01%; 95% CI, -0.03% to 0.3%).[114] (SOE: Insufficient)

DPP-4 Inhibitors Versus GLP-1 Receptor Agonists

Two short duration RCTs compared a DPP-4 inhibitor with a GLP-1 receptor agonist, favoring the GLP-1 receptor agonists.[73, 115] The first double-blind, moderately-sized RCT compared sitagliptin at 100 mg daily with exenatide 2 mg weekly for 26 weeks (calculated between-group difference in HbA1c of 0.4%; 95% CI, 0.07% to 0.49%) favoring exenatide.[73] A second open-label RCT, with 40 participants and lasting 24 weeks, compared sitagliptin at 50 mg daily with liraglutide titrated to 0.9 mg daily (calculated mean between-group difference in HbA1c of 1.3%; 95% CI, -0.6% to 3.2%) non-significantly favoring liraglutide.[115] (SOE: Low; GLP-1 receptor agonists favored)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Fourteen studies lasting less than one year compared metformin with the combination of metformin plus a thiazolidinedione (eight studies with rosiglitazone and six studies with pioglitazone)[55, 59, 67, 116-126] and showed a greater improvement in HbA1c with the combination therapy, in all the studies. The pooled between-group difference for all the studies combined had marked heterogeneity, but the meta-regression and stratified meta-analysis results showed consistent superiority of combination therapy (Table 5). The baseline HbA1c and dosing differences between arms were significant sources of heterogeneity. Studies with higher baseline HbA1c (HbA1c $\geq$ 8%) had greater between-group differences than studies with lower baseline HbA1c (HbA1c < 8%). Studies with smaller dosing differences between study arms had smaller between-group differences in HbA1c than studies with larger dosing differences between arms. One long study,[127] with 80 weeks of followup, compared metformin titrated to 2000 mg daily with metformin plus rosiglitazone titrated to 2000/8 mg daily. In that study, with around 5 percent loss to followup, the adjusted mean between-group difference in HbA1c favored combination therapy by 0.5 percent, consistent with the results in the shorter studies. (SOE: High; Combination of metformin plus a thiazolidinedione favored)

Table 5. Pooled mean between-group difference in HbA1c comparing metformin with a combination of metformin plus a thiazolidinedione stratified by baseline HbA1c and dosing differences

Variables	N of Studies	WMD (95% CI)	I^2	Summary
Baseline HbA1c <8%	7	0.43% (0.23% to 0.63%)	79%	Favored metformin + thiazolidinedione
Baseline HbA1c >=8%	7	0.88% (0.73% to 1.04%)	18%	Favored metformin + thiazolidinedione
Small dosing differences between study arms*	4	0.25% (0.16% to 0.34%)	0%	Favored metformin + thiazolidinedione
Large dosing differences between study arms*	10	0.79% (0.64% to 0.95%)	57%	Favored metformin + thiazolidinedione

CI = confidence interval; HbA1c = hemoglobin A1c; WMD = weighted mean difference

*Studies were grouped together that had similar between-group differences in study dosing between arms. This led to two categories: those studies with smaller and larger between-group differences in drug dosing. We used the DerSimonian and Laird random effects point estimate for the weighted mean difference of the large dosing differences since profile likelihood estimate results would not converge.

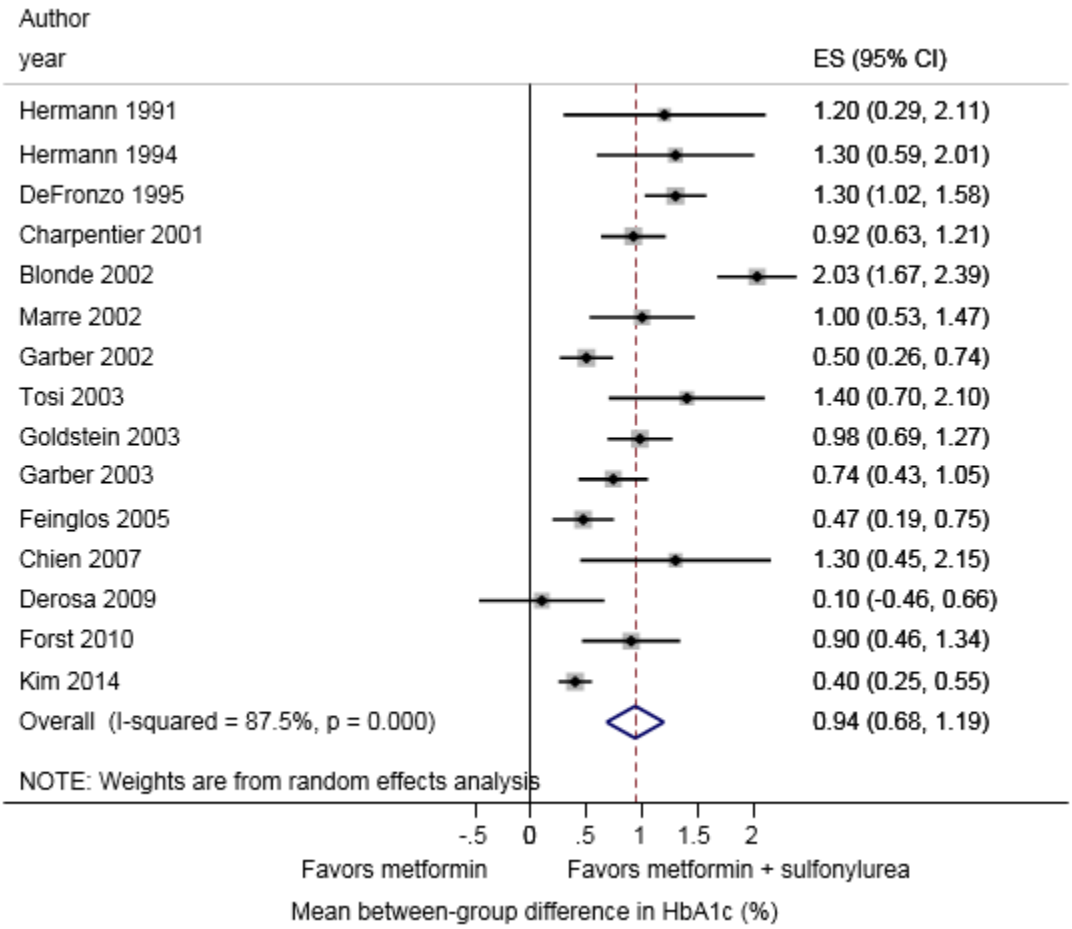
Metformin Versus a Combination of Metformin Plus a Sulfonylurea

Fifteen RCTs, each lasting less than one year, compared metformin with the combination of metformin plus a sulfonylurea, with all of the studies favoring the combination arm over monotherapy (pooled between-group difference, 0.9%; 95% CI, 0.7% to 1.2%) (Figure 8).[47, 55, 128-140]

No single study markedly influenced the results. Meta-regression was conducted due to substantial heterogeneity, but none of the *a priori* variables were found to be significant, including study duration, dosing differences, appropriate randomization, double blinding, baseline HbA1c, or whether the study reported on withdrawals and dropouts. The study by Blonde et al. showed the greatest between-group differences; this study used a high-dose combination and started with the highest baseline HbA1c compared with other studies.[131] The

study with the smallest between-group difference underdosed the metformin arm substantially in the metformin plus sulfonylurea arm.[55] Three of the six dose-response studies showed a dose-response gradient favoring greater reductions in HbA1c with a higher dose combination than with a lower dose combination.[131, 132, 134] One crossover study initially showed a difference between groups at the first crossover and then a negative rebound effect when changing the combination to monotherapy.[47] A study by Ahren et al. was excluded from the meta-analysis since the study duration was longer than the other studies.[141] This study, lasting 104 weeks, compared metformin at ≥ 1500 mg daily to the combination of metformin at ≥ 1500 mg daily plus glimepiride (up to 4 mg daily), and showed a between-group difference in HbA1c of 0.63 percent, favoring the combination arm, which was consistent with the results of the shorter studies included in the meta-analysis. (SOE: High; combination of metformin plus a sulfonylurea favored)

Figure 8. Pooled mean between-group difference in hemoglobin A1c comparing metformin with a combination of metformin plus a sulfonylurea



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

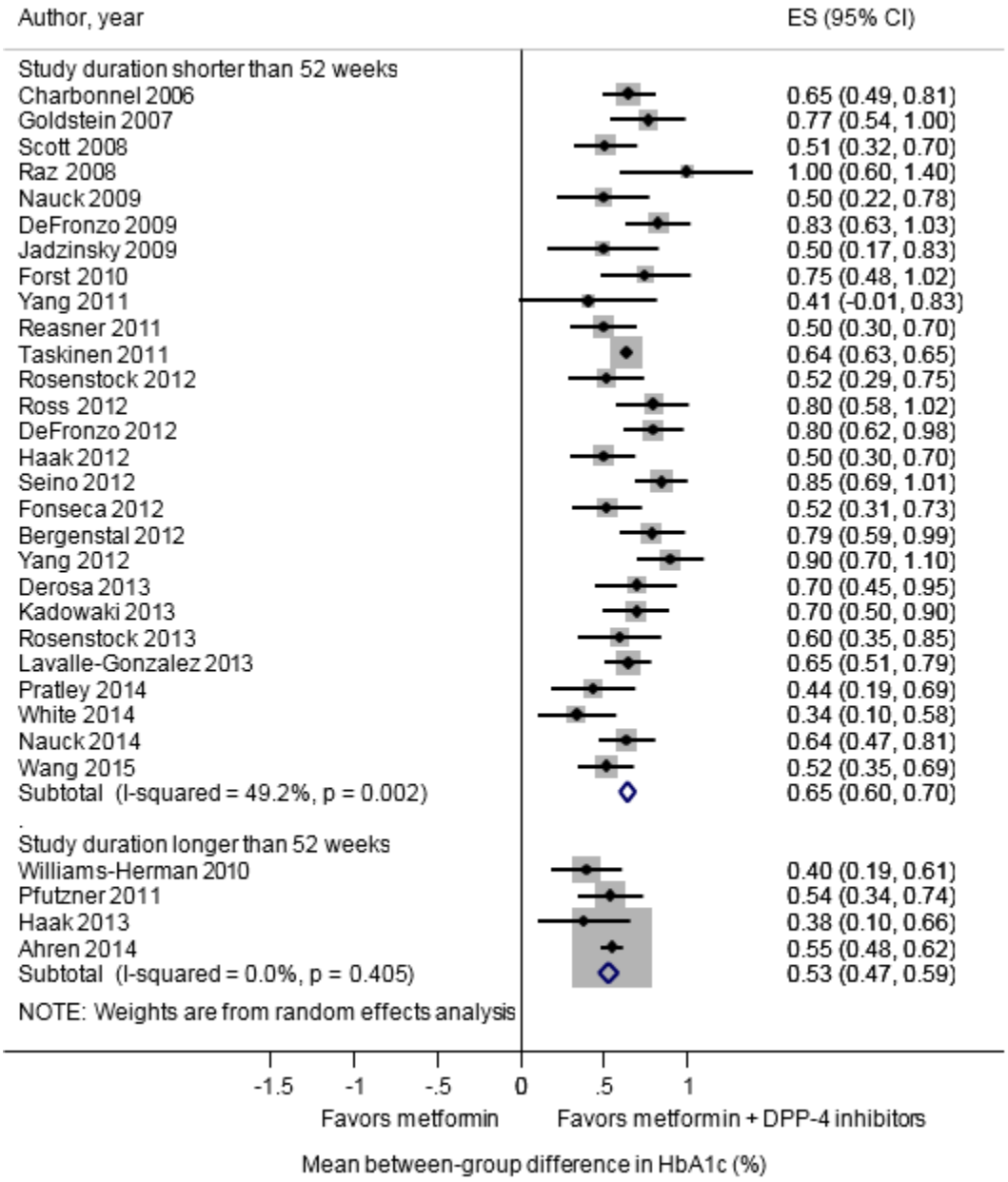
Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Twenty-seven RCTs, each lasting one year or less, directly compared metformin with the combination of metformin plus a DPP-4 inhibitor, with all favoring the combination arm (pooled between-group difference of 0.65%; 95% CI, 0.60% to 0.70%) (Figure 9).[51, 80, 83, 84, 86, 118, 126, 139, 142-160] No single study markedly influenced the results, and no substantial heterogeneity was identified.

Three short studies were not included in the meta-analysis due to dosing differences in two studies[161, 162] and median HbA1c being reported in the other study.[163] Two RCTs had 1000 mg more metformin in the monotherapy arm compared with the combination arm; therefore, these two studies[161, 162] had smaller between-group differences than the other studies. The 12-week study[163] reporting median HbA1c described a non-significant between-group difference in median HbA1c of 0.9% (p=0.1) favoring the combination arm of metformin (>1000 mg daily) plus sitagliptin (100 mg daily) over metformin alone (>1000 mg daily).

Four longer studies (two of which were extension studies), each lasting 76 to 104 weeks with 30 percent to 50 percent losses to followup, also compared metformin with metformin plus a DPP-4 inhibitor, with results consistent with the shorter studies.[85, 87, 141, 164] All four favored the combination arm (pooled between-group difference in HbA1c of 0.53%; 95% CI, 0.47% to 0.59%) (Figure 9). No single study markedly influenced the results, and no substantial heterogeneity was found. (SOE: High; Combination of metformin plus a DPP-4 inhibitor favored in the shorter duration studies) (SOE: Moderate; Combination of metformin plus a DPP-4 inhibitor favored in the longer duration studies)

Figure 9. Pooled mean between-group difference in hemoglobin A1c comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c

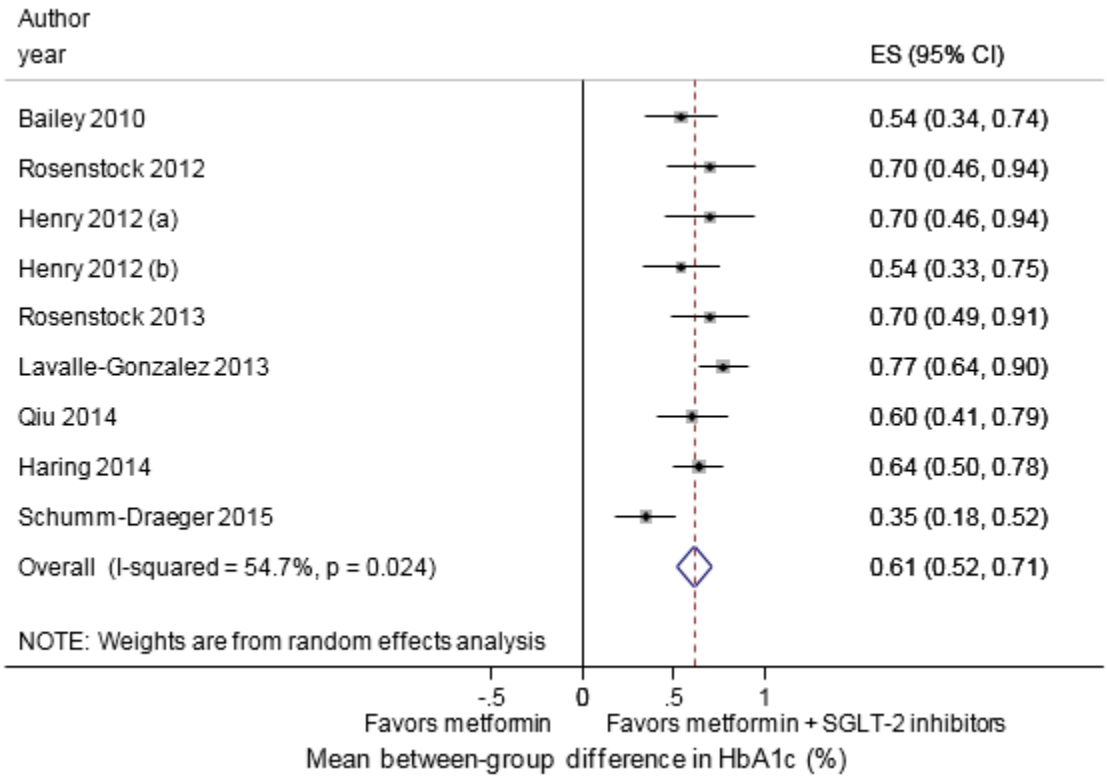
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Nine RCTs (reported in eight articles), each lasting less than one year, compared metformin alone with metformin plus an SGLT-2 inhibitor, with all studies favoring the combination arm (pooled between-group difference in HbA1c, 0.61%; 95% CI, 0.52% to 0.71%) (Figure 10).[88, 153, 156, 158, 165-168] No single study markedly influenced the results. Heterogeneity was identified

attributable to the Schumm-Draeger study which had the smallest between-group difference in HbA1c. No clear design differences exist between this study and the other studies in the meta-analysis, so we included it in the meta-analysis. Consistent with the meta-analysis results, two additional RCTs, each lasting 102 weeks, had statistically significant between-group differences in HbA1c of 0.4 percent and 0.8 percent, favoring the combination arms.[169, 170] (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 10. Pooled mean between-group difference in hemoglobin A1c comparing metformin with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Five short RCTs, each lasting less than one year, and one RCT, lasting 2 years, compared metformin with metformin plus a GLP-1 receptor agonist (albiglutide, liraglutide, dulaglutide, and exenatide), with all studies significantly favoring the combination arm over the monotherapy arm (range in between-group differences in HbA1c of 0.5% to 1.3%).[141, 159, 171-174] We did not combine these studies in a meta-analysis due to differences in baseline HbA1c, study duration, and drug dosing. The two studies with low mean baseline HbA1c of 6.3 percent and 7.2 percent had between-group differences in HbA1c of 0.5 percent,[172, 173] and the four studies with higher mean baseline HbA1c of around 8.0 percent had between-group differences in HbA1c ranging from 0.8 percent to 1.3 percent.[141, 159, 171, 174] The one study with a lower dose and higher dose

combination arm showed a dose-response relationship, with a smaller between-group difference in HbA1c of 0.5 percent in the lower dose combination and a larger between-group difference in HbA1c of 0.9 percent with the higher dose combination arm.[174] (SOE: Moderate; Combination of metformin plus a GLP-1 receptor agonist favored)

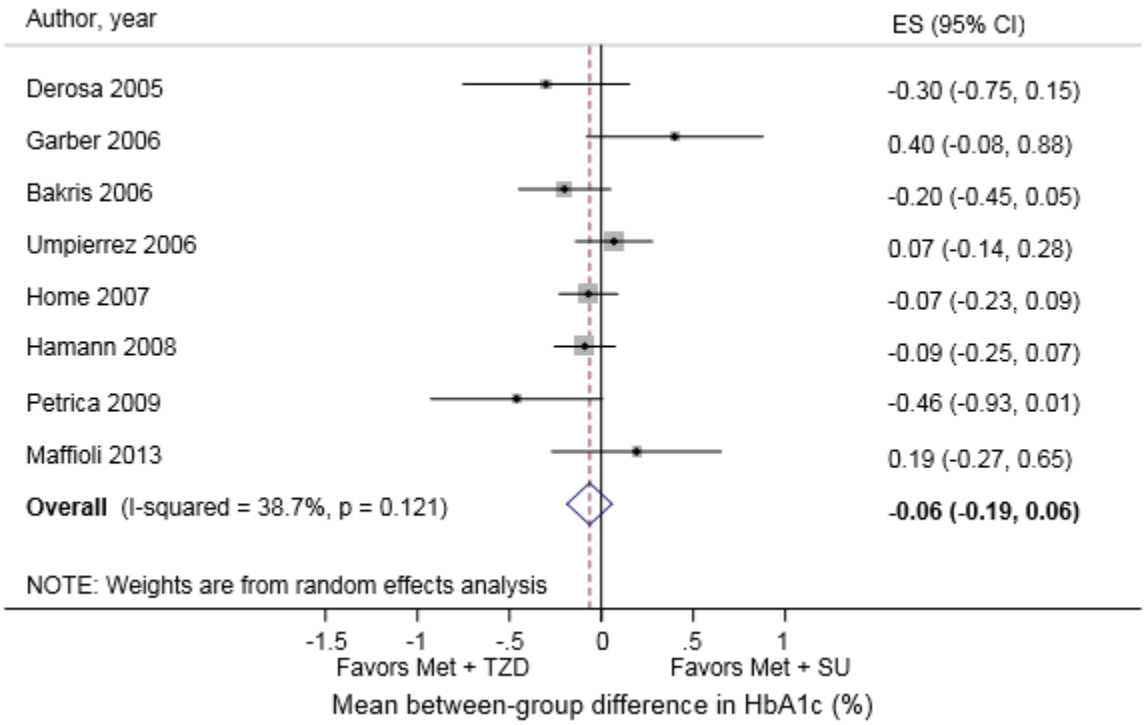
Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Eight comparably-dosed RCTs, each lasting less than one year, directly compared the combination of metformin plus a thiazolidinedione with metformin plus a sulfonylurea (pooled between-group difference in HbA1c of -0.06%; 95% CI, -0.19% to 0.06%) (Figure 11).[175-182] No single study markedly influenced the results, and no substantial heterogeneity was found. We excluded four studies from the meta-analysis due to dosing concerns within the studies.[55, 183-185] Two studies used lower doses in the metformin plus sulfonylurea arms than in the comparator arms and found between-group differences in HbA1c favoring the metformin plus thiazolidinedione arms (-0.3% in both studies).[55, 183] Two additional studies used submaximal sulfonylurea in the metformin plus sulfonylurea arm; one of the two studies favored the metformin plus thiazolidinedione arm. A sensitivity analysis including these four studies in the meta-analysis showed no marked differences in the pooled estimate and confidence interval, but more heterogeneity.

In the meta-analysis, we included the 18-month results from the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) study, since the study duration was comparable to the other included studies.[176] The RECORD study was a multicenter, open-label RCT evaluating 4,447 patients with type 2 diabetes and uncontrolled glycemia already on metformin or sulfonylurea monotherapy.[49, 176] The investigators randomly assigned subjects to the addition of rosiglitazone or to a combination of metformin and sulfonylurea. They reported glycemic control at a mean of 18 months for the first set of participants and a mean of 5.5 years after the start of the study for all included subjects not lost to followup.[49, 176] The between-group difference in HbA1c of -0.07 percent was small and not significant for the first 516 subjects with 18-month followup.[176] In the article reporting on the mean followup of 5.5 years in 2,222 subjects, the between-group difference in HbA1c of -0.29 percent significantly favored metformin plus rosiglitazone over metformin plus sulfonylurea.[49] (SOE: Moderate; Neither drug combination favored)

Figure 11. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea

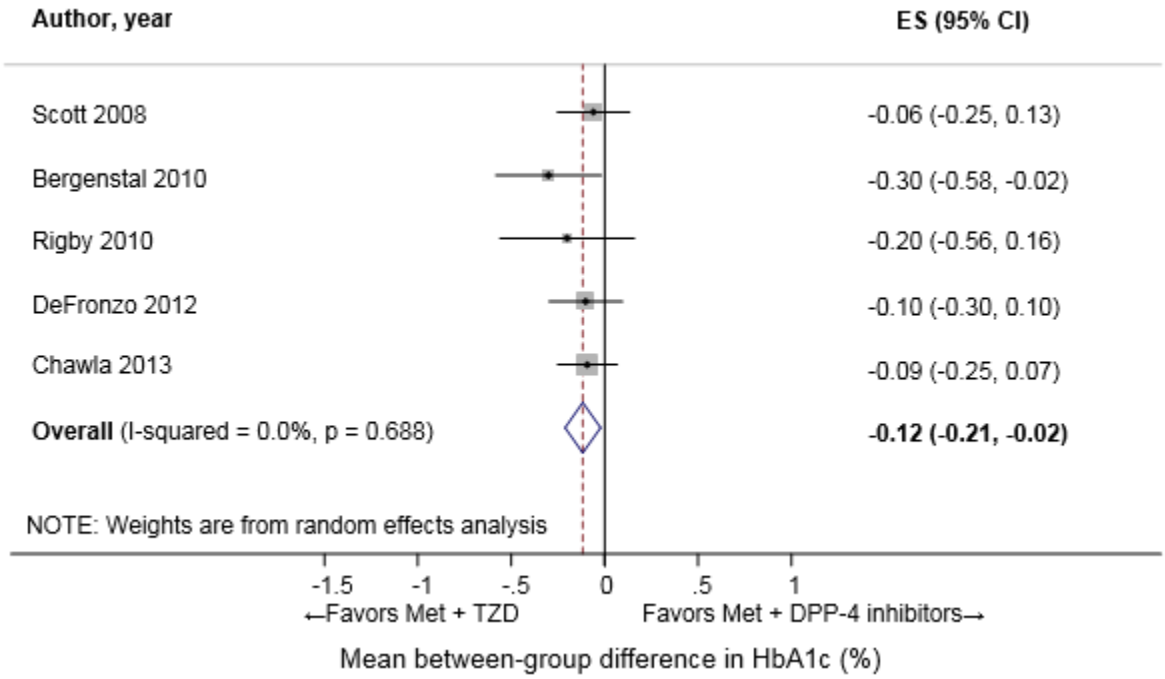


CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin; SU = sulfonylurea; TZD = thiazolidinedione
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Five short RCTs compared metformin plus rosiglitazone with the combination of metformin plus sitagliptin and slightly favored the metformin plus thiazolidinedione arms (pooled between-group difference in HbA1c, -0.12%; 95% CI, -0.21% to -0.02%) (Figure 12).[118, 126, 186-188] No substantial heterogeneity was identified in the meta-analysis. Removing the study by Bergenstal et al.[188] changed the confidence interval to non-significant (95% CI with Bergenstal et al. removed, -0.19% to 0.01%). This study[188] was not qualitatively different than the other studies, so we included it in the overall meta-analysis. This meta-analysis may underestimate the effect of metformin plus thiazolidinedione over metformin plus DPP-4 inhibitors, since two of the studies used lower drug doses in the metformin plus thiazolidinedione arms.[186, 187] (SOE: Moderate; Combination of metformin plus a thiazolidinedione favored)

Figure 12. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin; TZD = thiazolidinedione
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Two short RCTs, with adequate dosing in both arms, compared metformin plus thiazolidinediones (pioglitazone or rosiglitazone) with metformin plus a GLP-1 receptor agonist (exenatide) and had conflicting results.[188, 189] The 20-week RCT comparing a combination of metformin and rosiglitazone with the combination of metformin and exenatide showed no significant between-group differences in HbA1c (between-group difference, -0.1%; $P = 0.7$).[189] The 26-week RCT comparing the combination of metformin and pioglitazone with the combination of metformin and weekly exenatide favored the metformin plus exenatide arm (mean difference in HbA1c, 0.3%; 95 CI, 0.05% to 0.55%).[188] (SOE: Insufficient)

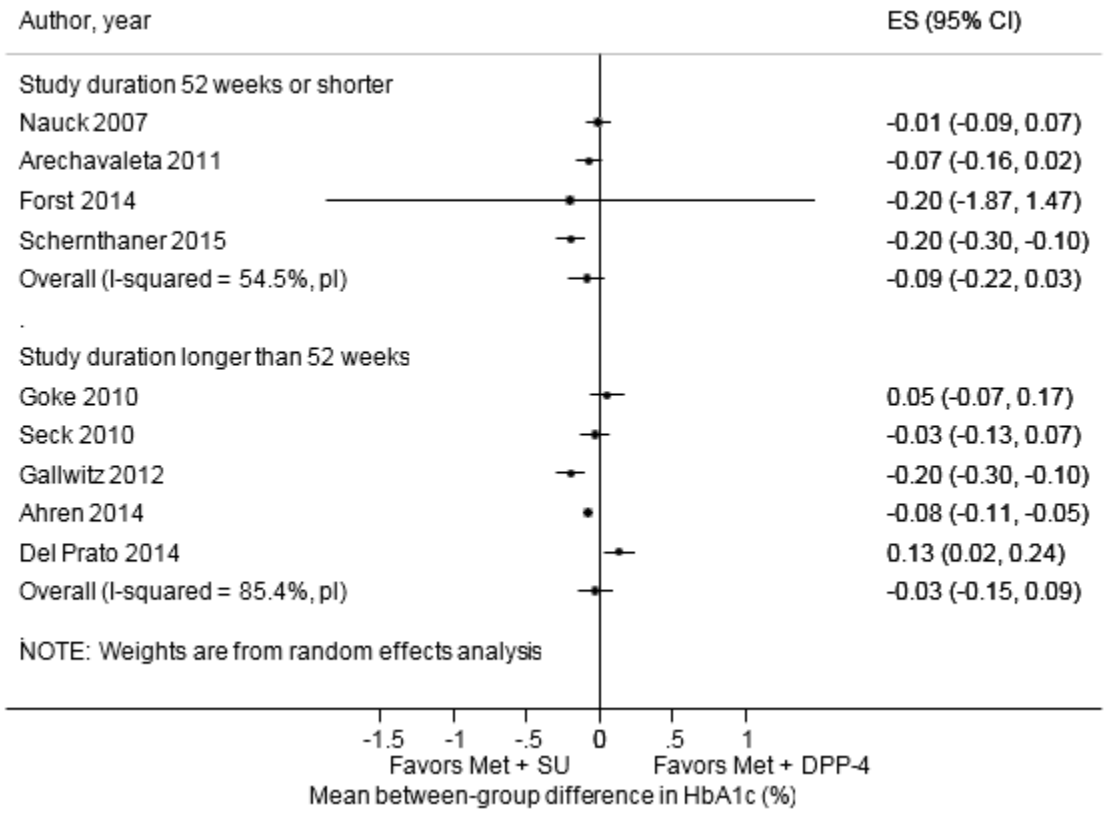
Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Nine studies (reported in ten articles) compared the combination of metformin plus sulfonylurea with metformin plus a DPP-4 inhibitor. We combined four RCTs, each lasting 1 year or less, comparing metformin plus a sulfonylurea with metformin plus a DPP-4 inhibitor, and found no significant between-groups differences in HbA1c (pooled between-group difference, -0.09%; 95 CI, -0.21% to 0.03%) (Figure 13).[190-193] However, all four RCTS used a moderate dose of sulfonylurea in the metformin plus sulfonylurea arms while using the maximum dose of the DPP-4 inhibitors. If we exclude the study by Nauck and colleagues,[192] the

pooled result would then significantly favor the combination of metformin plus sulfonylurea (pooled between group difference -0.13%, 95% CI -0.24% to -0.02%). However, there is no clear difference between this study and the other studies. No other study substantially changed the meta-analysis results. One additional short RCT was excluded from the meta-analysis, since we were unable to calculate a measure of variability.[139] This study reported a mean change from baseline in HbA1c that significantly favored the metformin plus sulfonylurea arm over the metformin plus DPP-4 inhibitor arm of -0.2%, despite a lower dose of the sulfonylurea.

Five longer studies, lasting 104 weeks and with over 20 percent loss to followup, also compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a DPP-4 inhibitor, and showed no significant pooled between-group difference in HbA1c (-0.03%; 95% CI, -0.15% to 0.09%) (Figure 13).[141, 194-197] However, all five RCTs titrated the sulfonylurea to a moderate dose and compared this to a fixed maximum dose of a DPP-4 inhibitor. One of the longer studies was an extension of a study included in the meta-analysis of the shorter studies.[192] No single study strongly influenced the results. (SOE: Low; Neither drug combination favored for both shorter and longer duration studies when comparing moderate dose sulfonylureas plus metformin with maximum dose DPP-4 inhibitors plus metformin)

Figure 13. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration

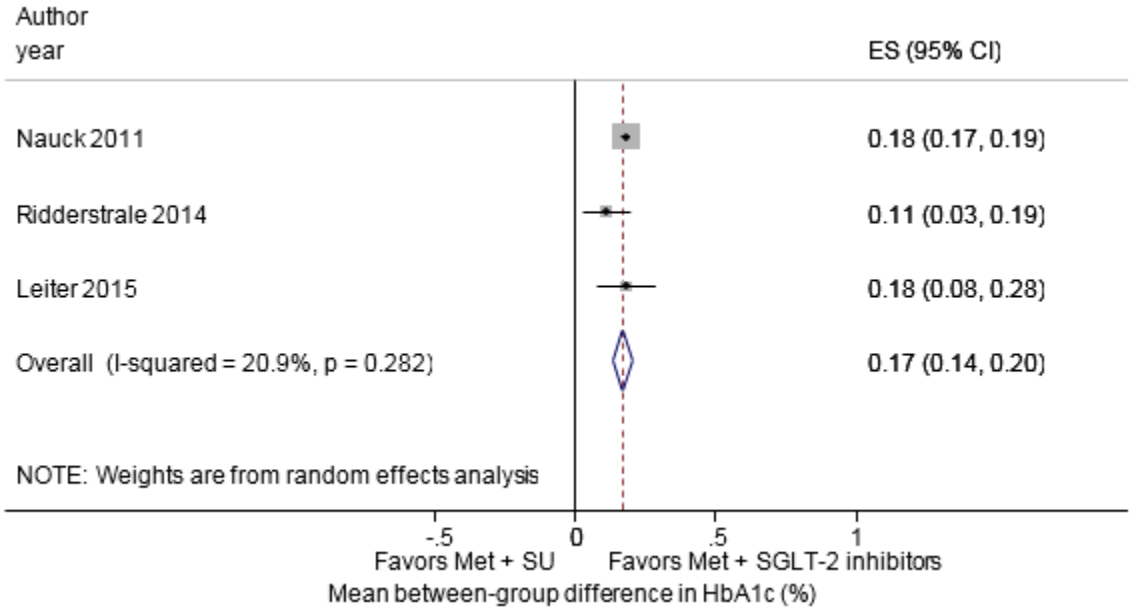


CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin; pl = profile likelihood estimate; SU = sulfonylurea
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95% CI for each study. The line at the bottom of the graph indicates the 95% CI for the profile likelihood pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Three RCTs (reported in five articles), each lasting 1 to 4 years, compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a SGLT-2 inhibitor (empagliflozin, dapagliflozin, or canagliflozin).[54, 198-201] All three studies lasting 2 years with 20 percent to 30 percent losses to followup favored the combination of metformin plus an SGLT-2 inhibitor (pooled between-group difference in HbA1c of 0.17%; 95% CI, 0.14% to 0.20%) (Figure 14).[199-201] No single study markedly influenced the results, and no substantial heterogeneity was identified. While all three studies used the maximum fixed dose of the SGLT-2 inhibitor, the sulfonylurea arms were all uptitrated to a moderate dose (mean glimepiride dose of 3 mg in one study, mean glimepiride dose of 5.6 mg in a second study, and a mean glipizide dose of 16 mg in the third study). One of the three studies also compared the combination of metformin plus a lower dose SGLT-2 inhibitor arm of canagliflozin 100 mg daily with the combination of metformin plus glimepiride (mean dose of 5.6 mg daily), reporting no significant between-group differences in HbA1c of 0.01%.[198] The 1-year and 4-year study findings were consistent with the 2-year results shown in the meta-analysis.[54, 198] (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 14. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

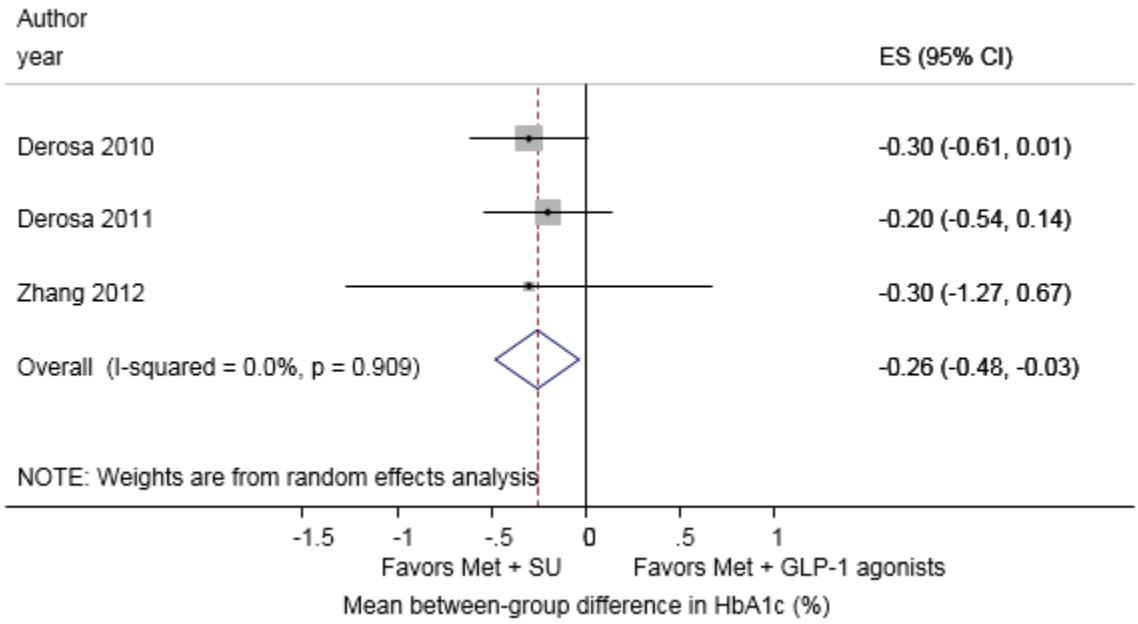
Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Six RCTs compared metformin plus sulfonylurea with metformin plus a GLP-1 receptor agonist, with conflicting results.[53, 141, 202-205] While no clear source of heterogeneity was

identified, intraclass differences could be part of the reason for the conflicting results. Three short-duration RCTs, each lasting one year or less, compared metformin plus sulfonylurea with metformin plus exenatide, all favoring the combination of metformin plus sulfonylurea despite submaximal doses of sulfonylureas being compared with maximal doses of daily exenatide (pooled between-group difference in HbA1c, -0.26%; 95% CI, -0.48% to -0.03%) (Figure 15).[202, 203, 205] No single study strongly influenced the results, and no substantial heterogeneity was identified. An additional longer duration RCT, excluded from the meta-analysis due to dosing and study duration differences, compared metformin plus low dose glimepiride (mean daily dose: 2 mg) with metformin plus high dose exenatide (mean daily dose: 17 micrograms) with about a 75 percent loss to followup among the treatment groups over 48 months. The primary outcome was time to treatment failure which was not clearly defined except to state that they were in line with the American Diabetes Association recommendations for requiring alternative treatment due to inadequate glycemic control. They also evaluated HbA1c using a mixed model repeated measures analysis at different time points and reported no significant between-group differences at 1 year. At 2 years, they reported a significant between-group difference in HbA1c, favoring the metformin plus exenatide group by 0.2 percent which was maintained at 3 years.[53]

Two RCTs also compared metformin plus a sulfonylurea with metformin plus other types of GLP-1 receptor agonists (albiglutide or liraglutide), with conflicting results.[141, 204] These were excluded from the meta-analysis due to dosing, drug type, and study duration differences. The first 16-week RCT compared metformin plus glimepiride (titrated to 4 mg daily) with similarly dosed metformin plus liraglutide (titrated to 1.8 micrograms daily), favoring the combination of metformin plus sulfonylurea (mean between-group difference, -0.3%; 95% CI, -0.34% to -0.27%).[204] The 104-week RCT, with over 30 percent loss to followup, compared metformin plus submaximal dose glimepiride (titrated to 4 mg daily) with the combination of metformin plus maximum dose albiglutide (titrated to 50 mg weekly), favoring the metformin plus albiglutide arm (mean between-group difference in HbA1c, 0.3%; 95% CI, 0.1% to 0.5%).[141] (SOE: Low; Combination of metformin plus exenatide favored; SOE: Insufficient for combination of metformin plus other GLP-1 receptor agonists)

Figure 15. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus daily exenatide



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); GLP-1 agonists = glucagon-like peptide-1 receptor agonist (here, all exenatide); HbA1c = hemoglobin A1c; Met = metformin; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a Basal Insulin

One small, open-label RCT, lasting 48 weeks, compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a basal insulin, showing no significant between-group differences in HbA1c of 0.1% (95% CI, -0.5% to 0.7%).[206] Patients were kept on their prior metformin doses and were randomized to uptitration of glimepiride (mean daily dose of 4 mg) versus uptitration of insulin glargine (mean daily dose of 23 units). Uptitration was stopped after reaching fasting plasma glucose titration goals.[206] (SOE: Insufficient)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a Premixed Insulin

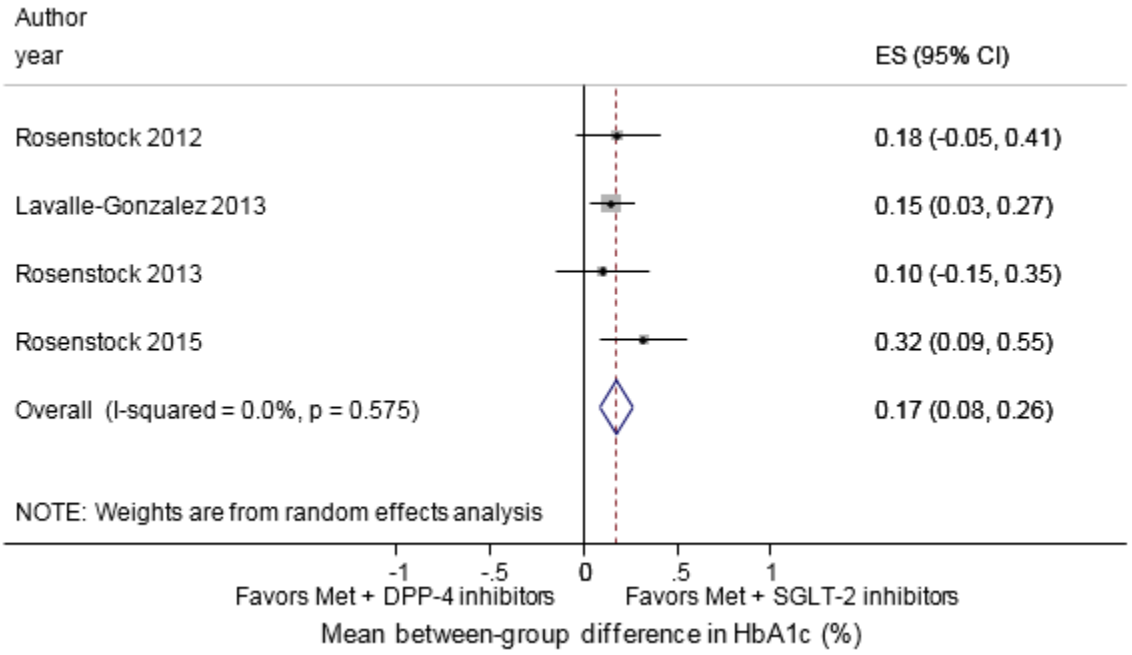
Two 16-week RCTs compared metformin plus glibenclamide with the combination of metformin plus a premixed insulin analogue – insulin aspart 70/30 in one study and insulin lispro 75/25 in the other study, with different results.[207, 208] These differences may have been due to differences in dosing of the medications. The RCT[207] that showed no significant between-group differences in HbA1c (-0.11%, p = 0.238) reported the mean total dose for each combination arm, while the other RCT, which significantly favored the metformin plus premixed insulin analogue (insulin aspart 70/30) arm over the metformin plus sulfonylurea arm (between-group difference of 0.46%, p = 0.027), did not clearly report mean total or maximum doses.[208] Another possible difference may have been the type of premixed insulin analogue. (SOE: Insufficient)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Four short, sufficiently-dosed RCTs, each lasting one year or less, compared the combination of metformin plus a DPP-4 inhibitor (sitagliptin or saxagliptin) with the combination of metformin plus an SGLT-2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin). The studies significantly favored the combination of metformin plus an SGLT-2 inhibitor (pooled between-group difference in HbA1c, 0.17%; 95% CI, 0.08% to 0.26%) (Figure 16).[153, 156, 158, 209] No single study strongly influenced the results, and no substantial heterogeneity was found in the meta-analysis.

One longer RCT, lasting 90 weeks and with less than 10 percent loss to followup, comparing metformin plus sitagliptin with metformin plus empagliflozin at maximum doses was consistent with the shorter studies' pooled results, favoring slightly the metformin plus empagliflozin arm (mean between-group difference in HbA1c, 0.2%; 95% CI, 0.0% to 0.5%).[90] (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 16. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus an SGLT-2 inhibitor



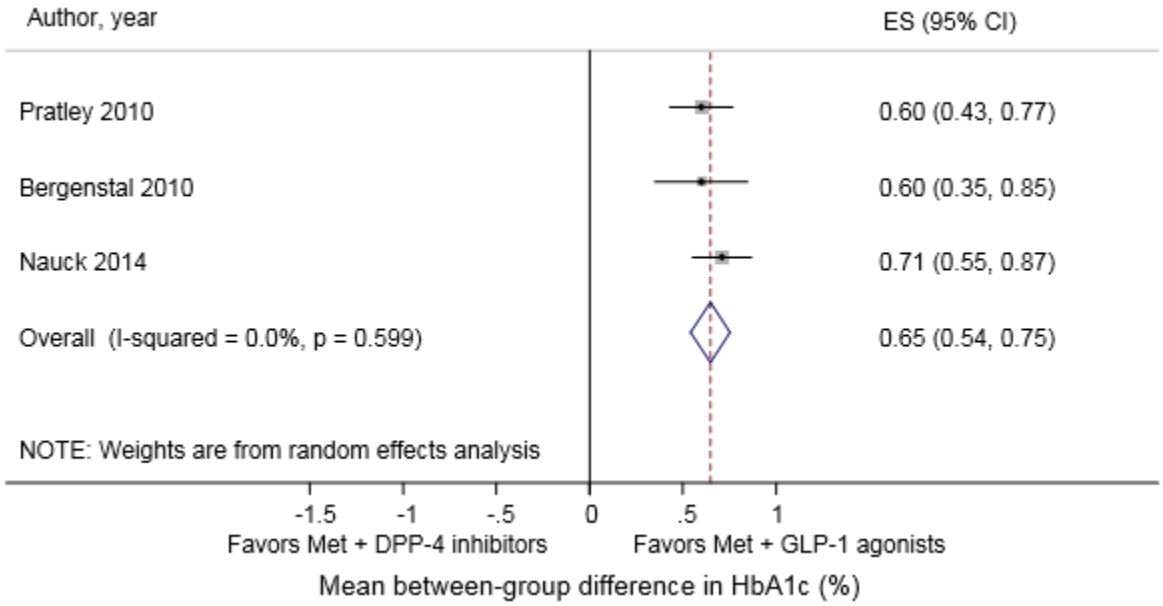
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Three adequately-dosed RCTs, lasting one year or less, compared the combination of metformin plus sitagliptin with the combination of metformin plus a GLP-1 receptor agonist (liraglutide or exenatide). All three RCTs significantly favored the combination of metformin plus a GLP-1 receptor agonist (pooled between-group difference in HbA1c, 0.65%; 95% CI,

0.54% to 0.75%) (Figure 17).[159, 188, 210] No single study markedly influenced the meta-analysis results, and no substantial heterogeneity was identified. One longer study, lasting 104 weeks, compared metformin plus sitagliptin with metformin plus albiglutide, significantly favoring the metformin plus albiglutide arm by 0.4 percent, consistent with the shorter studies' pooled results.[141] (SOE: Moderate; Combination of metformin plus a GLP-1 receptor agonist favored)

Figure 17. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 receptor agonist



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; Met = metformin
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 for the random-effects pooled estimate.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a Basal Insulin

One moderately-sized, 24-week RCT compared metformin plus sitagliptin (100 mg daily) with metformin plus insulin glargine titrated to 0.5 units per kg, significantly favoring the metformin plus insulin glargine arm (mean between-group difference in HbA1c of 0.59%; 95% CI, 0.42% to 0.76%).[211] (SOE: Low; Combination of metformin plus a basal insulin favored)

Combination of Metformin Plus a GLP-1 Receptor Agonist Versus a Combination of Metformin Plus a Basal Insulin

One 26-week RCT compared metformin plus exenatide (2 mg weekly) with metformin plus glargine insulin, with a reported between-group difference in HbA1c favoring the combination of metformin plus exenatide by -0.2% (95% CI, -0.3% to -0.02%).[212] (SOE: Insufficient)

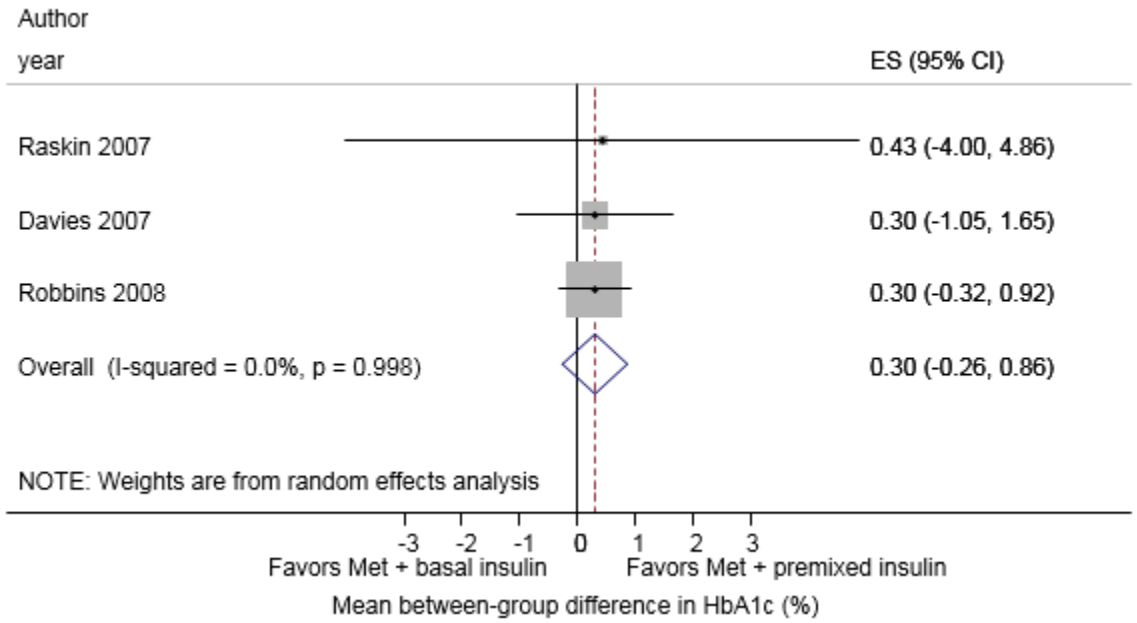
Combination of Metformin Plus a GLP-1 Receptor Agonist Versus a Combination of Metformin Plus a Premixed Insulin

One moderately-sized RCT, lasting 26 weeks, compared the combination of metformin plus exenatide (titrated to 20 micrograms) with the combination of metformin plus premixed insulin (titrated to glucose target, mean dose 28 units), showing no significant between-group difference in HbA1c of 0.14% (95% CI, -0.003% to 0.29%).[213] (SOE: Insufficient)

Combination of Metformin Plus a Basal Insulin Versus a Combination of Metformin Plus a Premixed Insulin

Three RCTs directly compared the combination of metformin plus basal insulin with the combination of metformin plus premixed insulin, showing no between-group differences in HbA1c (pooled between-group difference, 0.3%; 95% CI, -0.3% to 0.9%) (Figure 18).[214-216] No single study strongly influenced the results, and no substantial heterogeneity was found. (SOE: Low; Neither drug favored)

Figure 18. Pooled mean between-group difference in hemoglobin A1c comparing a combination of metformin plus a basal insulin with a combination of metformin plus a premixed insulin



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); HbA1c = hemoglobin A1c; Met = metformin

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Strength of Evidence for Hemoglobin A1c

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 6, Table 7, and Table 8 and summarized in the Key Points. All studies were RCTs. Study limitations for most comparisons were low or medium with only three comparisons having high study limitations due to lack of blinding, lack of description of withdrawals and dropouts, or very high losses to followup. Where quality influences the results,

we describe that under the appropriate comparisons. In general, we did not find strong differences in outcomes in the lower versus higher quality studies. We did not find any evidence of publication bias using the Begg's and Egger's tests in most of the comparisons for HbA1c. A few of the monotherapy versus combination therapy comparisons had a statistically significant results on the publication bias test; however, these comparisons are likely to be missing both large and small negative studies favoring monotherapy. Therefore, we did not feel these statistically significant results represented a true publication bias. We also did not find any evidence of publication bias or reporting bias in the grey literature review which would change the overall conclusions. The grey literature was consistent with our findings for each of the comparisons, except for two comparisons (metformin versus DPP-4 inhibitors and metformin plus sulfonylurea versus metformin plus SGLT-2 inhibitors) where each had one study with results conflicting with the published results. These two studies under-dosed one of the study arms, making it more likely that conflicting results were from differing doses as opposed to publication bias. Only three studies did not report a measure of dispersion; therefore, we were able to combine most of the studies in meta-analyses, where appropriate.

Table 6. Strength of evidence domains for monotherapy comparisons in terms of hemoglobin A1c among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. TZD	25 (7365)	Medium	Consistent	Direct	Precise	Undetected	High	Neither drug favored; -0.04% (-0.11% to 0.03%)
Metformin vs. SU‡	NA	NA	NA	NA	NA	NA	High	Neither drug favored; 0.1% (-0.1% to 0.3%)
Metformin vs. DPP-4 inhibitors	6 (6700)	Low	Consistent	Direct	Precise	Undetected	High	Metformin favored-0.43% (-0.55% to -0.31%)
Metformin vs. SGLT-2 inhibitors	3 (1633)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither drug favored
Metformin vs. GLP-1 receptor agonists	3 (1089)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither drug favored
TZD vs. SU	17 (6212)	Medium	Consistent	Direct	Precise	Undetected	High	Neither drug favored; -0.04% (-0.13% to 0.06%)
TZD vs. DPP-4 inhibitors	3 (1686)	Low	Inconsistent	Direct	Imprecise	Suspected†	Insufficient¶‖	Unable to determine
TZD vs. GLP-1 receptor agonists	2 (1048)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
SU vs. DPP-4 inhibitors	3 (1271)	Low	Inconsistent	Direct	Imprecise	Suspected‡	Insufficient‖	Unable to determine
SU vs. GLP-1 receptor agonists	4 (2056)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient§	Unable to determine
DPP-4 inhibitors vs. SGLT-2 inhibitors	1 (899)	Low	Unable to determine	Direct	Imprecise	Undetected	Insufficient	Unable to determine
DPP-4 inhibitors vs. GLP-1 receptor agonists	2 (860)	Medium	Consistent	Direct	Imprecise	Undetected	Low	GLP-1 receptor agonist favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; NA = not applicable; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating hemoglobin A1c.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.

‡ We did not re-evaluate hemoglobin A1c for the comparison of metformin with sulfonylureas, because we previously rated this comparison as having high strength of evidence.[16]
¶ For thiazolidinediones versus DPP-4 inhibitors, we graded the strength of evidence as insufficient, since there was only one comparably-dosed study which used maximum doses in each arm. We suspected reporting bias, since one study was found in the grey literature which favored thiazolidinediones while two of the three published studies showed no significant difference between-groups in hemoglobin A1c but underdosed the thiazolidinedione arms compared to the DPP-4 inhibitor arms.
‖ For sulfonylureas versus DPP-4 inhibitors, we graded the strength as insufficient, since two of the three studies minimally favored sulfonylureas while one study did not favor either medication. Two additional studies found in the grey literature minimally favored sulfonylurea. Probably, sulfonylurea is mildly favored overall. We will be able to form a more formative opinion by the final report, since these two studies will be included in the updated search we will do between the draft and final report.
§ For sulfonylurea versus GLP-1 receptor agonist, only two comparably-dosed studies were identified and each showed different results. The two non-comparably-dosed studies favored the GLP-1 receptor agonist.

Table 7. Strength of evidence domains for metformin versus metformin-based combination comparisons in terms of hemoglobin A1c among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + TZD	15 (6090)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin +TZD favored; range in pooled mean between-group differences in HbA1c, 0.3% to 0.9%
Metformin vs. metformin + SU	17 (5210)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SU favored; 0.9% (0.7% to 1.2%)
Metformin vs. metformin + DPP-4 inhibitors (shorter duration studies)	30 (18,056)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin + DPP-4 inhibitor favored; 0.65% (0.6% to 0.7%)
Metformin vs. metformin + DPP-4 inhibitors (longer duration studies)	4 (4013)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + DPP-4 inhibitor favored; 0.5% (0.47% to 0.6%)
Metformin vs. metformin + SGLT-2 inhibitors	9 (5778)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitor favored; 0.6% (0.5% to 0.7%)
Metformin vs. metformin + GLP-1 receptor agonists	5 (2556)	Medium	Inconsistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 receptor agonist; range in between-group differences in HbA1c, 0.5% to 1.3%

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; HbA1c = hemoglobin A1c; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating hemoglobin A1c.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.

Table 8. Strength of evidence domains for metformin-based combination comparisons in terms of hemoglobin A1c among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + TZD vs. metformin +SU	14 (3294)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Neither drug combination favored; -0.1% (-0.2% to 0.1)
Metformin + TZD vs. metformin +DPP-4 inhibitors	5 (2413)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + TZD favored; -0.1% (-0.2% to -0.02%)
Metformin + TZD vs. metformin +GLP-1 receptor agonists	2 (604)	Low	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + SU vs. metformin +DPP-4 inhibitors (shorter duration studies)	5 (3300)	Medium	Inconsistent	Direct	Precise	Undetected	Low	Neither drug combination favored
Metformin + SU vs. metformin +DPP-4 inhibitors (longer duration studies)	5 (7270)	High	Consistent	Direct	Precise	Undetected	Low	Neither drug combination favored
Metformin + SU vs. metformin +SGLT-2 inhibitors (longer duration studies)	3 (3815)	Low	Consistent	Direct	Precise	Undetected	Moderate	Metformin + SGLT-2 inhibitor favored; 0.2% (0.1% to 0.2%)
Metformin + SU vs. metformin +GLP-1 receptor agonists	7 (4375)	Medium	1. Consistent for Met + SU vs Met + exenatide 2. Inconsistent for Met + SU vs Met + other GLP-1 receptor agonist	Direct	Precise	Undetected	Low for #1 and insufficient for #2	1. Metformin + exenatide favored 2. Unable to determine
Metformin + SU vs. metformin + basal insulin	1 (75)	High	Unable to determine	Direct	Imprecise	Undetected	Insufficient	Unable to determine

Table 8. Strength of evidence domains for metformin-based combination comparisons in terms of hemoglobin A1c among adults with type 2 diabetes (continued)

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + SU vs. metformin + premixed insulin	2 (827)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + DPP-4 inhibitors vs. metformin +SGLT-2 inhibitors	4 (3423)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + SGLT-2 inhibitor favored; 0.2% (0.1% to 0.3%)
Metformin + DPP-4 inhibitors vs. metformin +GLP-1 receptor agonists	4 (3322)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 receptor agonist favored; 0.7% (0.5% to 0.8%)
Metformin + DPP-4 inhibitors vs. metformin + basal insulin	1 (515)	Medium	Unable to determine	Direct	Precise	Undetected	Low	Metformin + basal insulin favored
Metformin + GLP-1 receptor agonists vs. metformin + basal insulin	1 (321)	Medium	Unable to determine	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + GLP-1 receptor agonists vs. metformin + premixed insulin	1 (363)	High	Unable to determine	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + basal insulin vs. metformin + premixed insulin	3 (530)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating hemoglobin A1c.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Weight

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

In the prior report, we graded the evidence as high[16] that metformin was significantly favored, with weight gain in the thiazolidinedione arms and weight loss in the metformin arms. Therefore, we did not re-evaluate this comparison for weight. (SOE: High; Metformin favored)

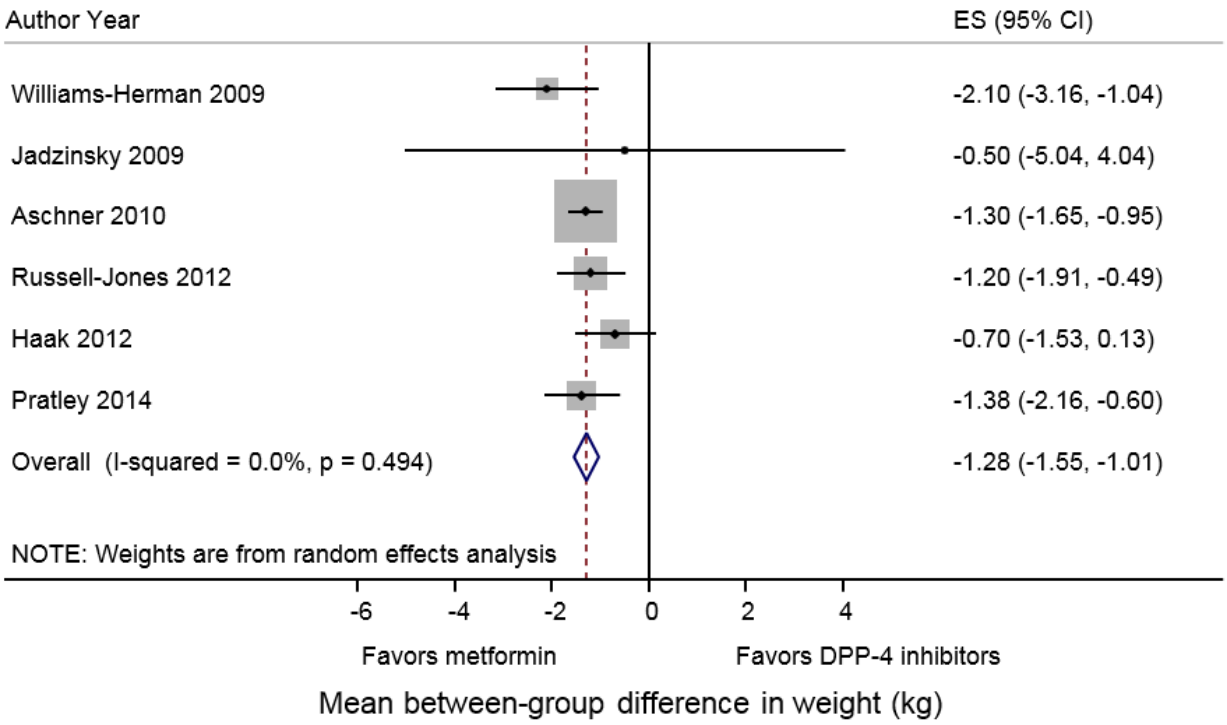
Metformin Versus Sulfonylureas

In the prior report, we graded the evidence as high[16] that metformin was significantly favored, with weight gain in the sulfonylurea arms and mild weight loss in the metformin arms. Therefore, we did not re-evaluate this comparison for weight. (SOE: High; Metformin favored)

Metformin Versus DPP-4 Inhibitors

Six short RCTs (reported in nine articles) compared metformin with DPP-4 inhibitors, reporting greater reductions in weight with metformin (pooled between-group difference, -1.3 kg; 95% CI, -1.6 kg to -1.0 kg) (Figure 19).[73, 80-87] No substantial heterogeneity was found in the meta-analysis, and no single study markedly influenced the results. Two RCTs (in three articles) were reported as extension studies.[81, 85, 87] The extension studies, lasting 76 weeks and 104 weeks and with losses to followup ranging between 20 percent to 76 percent, all favored metformin over the DPP-4 inhibitors (between-group differences of -0.7 kg to -2.9 kg), consistent with the meta-analysis results from the shorter studies. Three RCTs had a lower dose and higher dose metformin arm.[84-86] The higher dose metformin arms in two of the studies which compared metformin with alogliptin and sitagliptin both showed greater reductions in weight than the studies comparing lower dose metformin arms with alogliptin and sitagliptin.[84, 85] The third RCT, comparing a low dose and high dose metformin arm with linagliptin, did not show this dose response.[86] (SOE: High; Metformin favored)

Figure 19. Pooled mean between-group difference in weight comparing metformin with DPP-4 inhibitors



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus SGLT-2 Inhibitors

Two 24-week (reported in the same article) and one 90-week RCTs compared metformin with an SGLT-2 inhibitor (dapagliflozin or empagliflozin), showing greater reductions in weight with the SGLT-2 inhibitors (range of between-group differences in weight of -1.3 kg to -1.4 kg).[88, 90] These between-group differences were statistically significant in two of the three RCTs.[88] (SOE: Moderate; SGLT-2 inhibitors favored)

Metformin Versus GLP-1 Receptor Agonists

Three studies, each lasting one year or less, compared metformin with a GLP-1 receptor agonist, with conflicting effects on weight.[73, 91, 92] We did not combine the studies in a meta-analysis due to study duration and dosing differences. Each of the three studies, lasting 24 to 52 weeks, compared metformin at 2000 to 2500 mg with a GLP-1 receptor agonist at maximum doses (exenatide 20 micrograms daily in the first study, exenatide 2 mg weekly in the second study, and dulaglutide 1.5 mg weekly in the third study). The first comparably-dosed, 26-week RCT of metformin titrated to 2500 mg daily compared with a fixed dose of 2 mg of exenatide weekly reported a mean between-group difference in weight of 0 kg (95% CI, -0.6 kg to 0.6 kg).[73] The second 26-week RCT compared metformin titrated to 2000 mg with exenatide (10 micrograms twice daily).[92] This RCT reported a mean between-group difference of 2.0 kg, favoring the GLP-1 receptor agonist arm (95% CI, 1.2 kg to 2.8 kg).[92] The last 52-week RCT compared metformin titrated to 2000 mg with dulaglutide of 1.5 mg weekly, and reported a mean

between-group difference in weight favoring the metformin arm of -0.7 kg (95% CI, -1.4 kg to -0.03 kg).[91] (SOE: Insufficient)

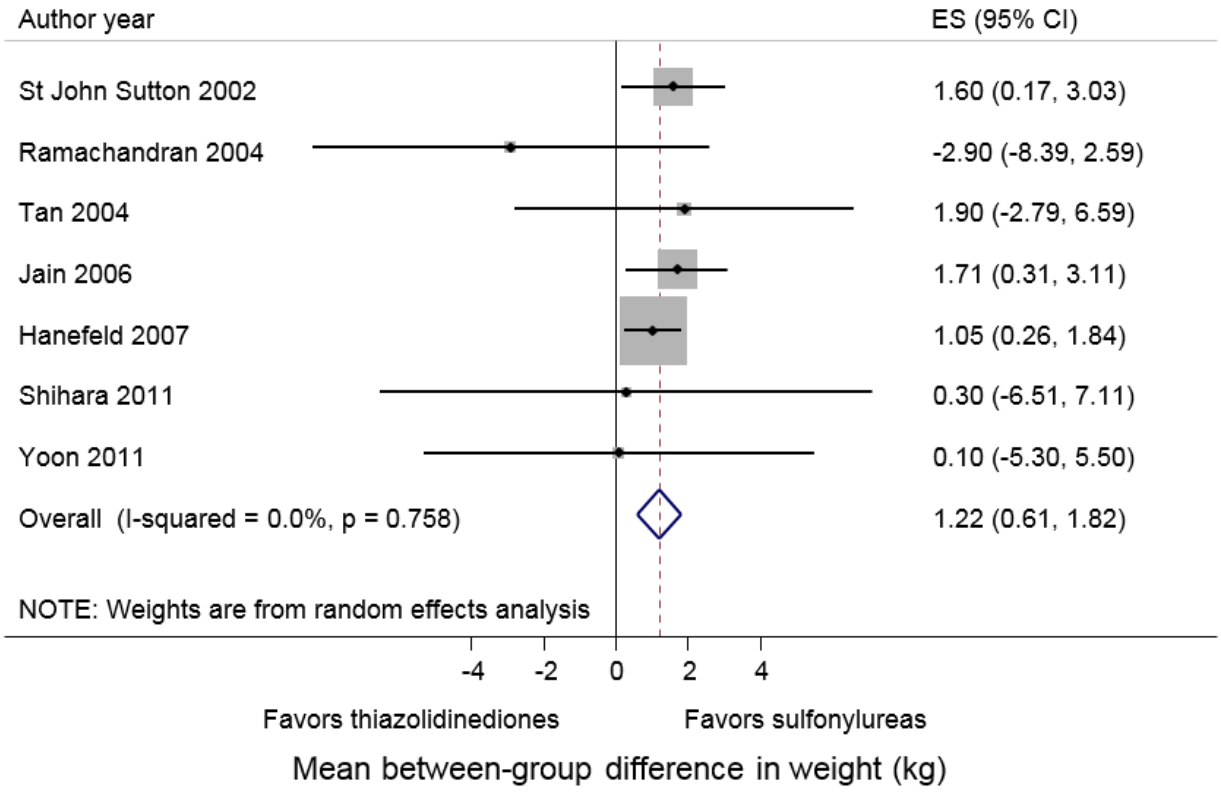
Thiazolidinediones Versus Sulfonylureas

Seven studies, each lasting one year or less, compared a thiazolidinedione to a sulfonylurea, showing higher weight gain in the thiazolidinedione arms, with a pooled between-group difference of 1.2 kg (95% CI, 0.6 kg to 1.8 kg) (Figure 20).[61, 74, 94, 95, 100, 103, 217] No single study markedly influenced the results, and no substantial heterogeneity was found.

One study showed a dose-response relationship between rosiglitazone and weight; patients treated with 4 mg per day of rosiglitazone gained 1.8 kg and those treated with 8 mg per day gained 3.0 kg, over 52 weeks compared with the glibenclamide arm which gained 1.9 kg.[94]

We excluded two RCTs from the meta-analysis due to their longer durations of 3 to 4 years.[50, 52] Both RCTs had results consistent with the meta-analysis. As mentioned previously, the ADOPT study, with >50 percent loss to followup, evaluated the long-term glycemic control of metformin, rosiglitazone, and glyburide monotherapy as initial treatment for adults with type 2 diabetes, with weight as a secondary outcome.[50] The between-group difference between rosiglitazone and glyburide was consistent with the results of the meta-analysis of the shorter studies, favoring sulfonylureas after approximately 5 years of followup (mean between-group difference, 2.5 kg; 95% CI, 2.0 kg to 3.1 kg). Of note, individuals in the glyburide arm gained weight over the first year and then stabilized, while those in the rosiglitazone arm had continued weight gain throughout the study. The second large, 3-year, multicenter study comparing pioglitazone with glibenclamide, also having > 50 percent losses to followup, showed a 5.2 kg weight gain in the pioglitazone-treated group and a 0.9 kg weight gain in the glibenclamide-treated group.[52] (SOE: Moderate; Sulfonylurea favored)

Figure 20. Pooled mean between-group difference in weight comparing thiazolidinediones with sulfonylureas



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Thiazolidinediones Versus DPP-4 Inhibitors

Two 26-week RCTs compared thiazolidinediones with DPP-4 inhibitors; both studies significantly favored DPP-4 inhibitors with a mean between-group difference of 2.3 kg and 2.5 kg.[73, 104] The thiazolidinedione arms increased weight by around 1.8 kg while the DPP-4 inhibitor arms decreased weight by around 0.5 kg. (SOE: Moderate; DPP-4 inhibitors favored)

Thiazolidinediones Versus GLP-1 Receptor Agonists

Two comparably-dosed RCTs compared thiazolidinediones (pioglitazone) with GLP-1 receptor agonists (exenatide), with both favoring exenatide by 3.5 kg. One double-blind moderately-sized RCT compared pioglitazone titrated to 45 mg daily with exenatide 2 mg weekly.[73] After 26 weeks, the calculated between-group difference in weight favored exenatide by 3.5 kg (95% CI, 2.8 kg to 4.2 kg).[73] The pioglitazone arm increased weight by 1.5 kg, and the exenatide arm decreased weight by 2 kg. The second open-label RCT compared pioglitazone at 45 mg daily with exenatide 10 ug twice daily. After 48 weeks, the calculated mean between-group difference in weight favored exenatide by 3.5 kg (95% CI, 2.4 kg to 4.6 kg).[105] (SOE: Moderate; GLP-1 receptor agonists favored)

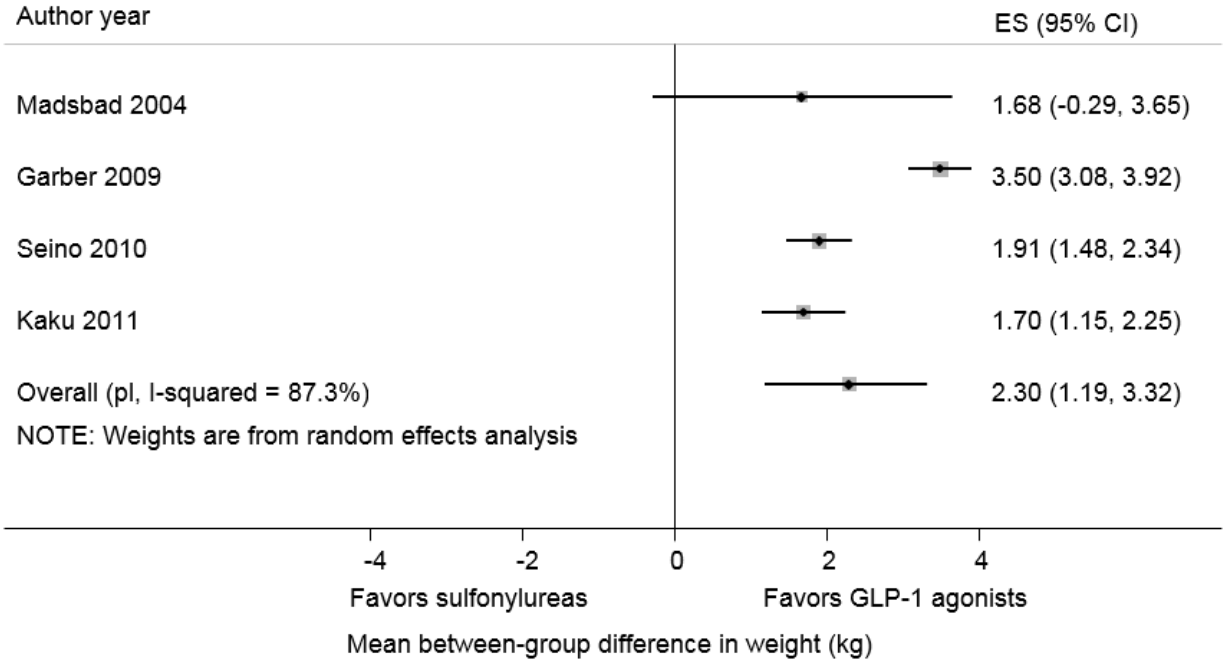
Sulfonylureas Versus DPP-4 Inhibitors

Three RCTs, each lasting 54 weeks or less, compared a sulfonylurea (glipizide or glimepiride) with a DPP-4 inhibitor (sitagliptin or linagliptin) and favored the DPP-4 inhibitor arms (range in mean between-group differences of 0.9 kg to 1.8 kg).[106-108] This difference was significant in two of the three studies; one study did not provide sufficient data to assess.[108] We did not combine these studies due to dosing and study population differences. Sulfonylureas increased weight by about 1.2 kg, and the DPP-4 inhibitors decreased weight by around 0.4 kg, in these studies. (SOE: Low; DPP-4 inhibitors favored)

Sulfonylureas Versus GLP-1 Receptor Agonists

Four RCTs comparing sulfonylureas directly with liraglutide showed greater weight gain with a sulfonylurea (pooled mean between-group difference, 2.3 kg; 95% CI, 1.2 kg to 3.3 kg) (Figure 21).[109-112] No single study strongly influenced the results. Substantial heterogeneity was found. Potential sources of heterogeneity were dosing differences, study duration differences, and differences in baseline weight. The one study with the largest between-group difference in weight[112] lasted at least 24 weeks longer than the other two studies, used medications titrated to the maximum dose in both arms, and started with a higher baseline BMI. (SOE: Moderate; GLP-1 receptor agonists favored)

Figure 21. Pooled mean between-group difference in weight comparing sulfonylureas with GLP-1 receptor agonists



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); GLP-1 = glucagon-like peptide-1; kg = kilogram; pl = profile likelihood estimate

Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

One double-blind, moderately-sized, 24-week RCT compared the DPP-4 inhibitor, sitagliptin at 100 mg daily, with the SGLT-2 inhibitor, empagliflozin at 10 mg and 25 mg daily. The results significantly favored the empagliflozin arms (calculated mean between-group difference of 2.5 kg and 2.7 kg for the low dose and high dose empagliflozin arms, respectively).[114] The sitagliptin-treated patients maintained weight, and the empagliflozin-treated patients decreased weight, over the 24 weeks. (SOE: Moderate; SGLT-2 inhibitors favored)

DPP-4 Inhibitors Versus GLP-1 Receptor Agonists

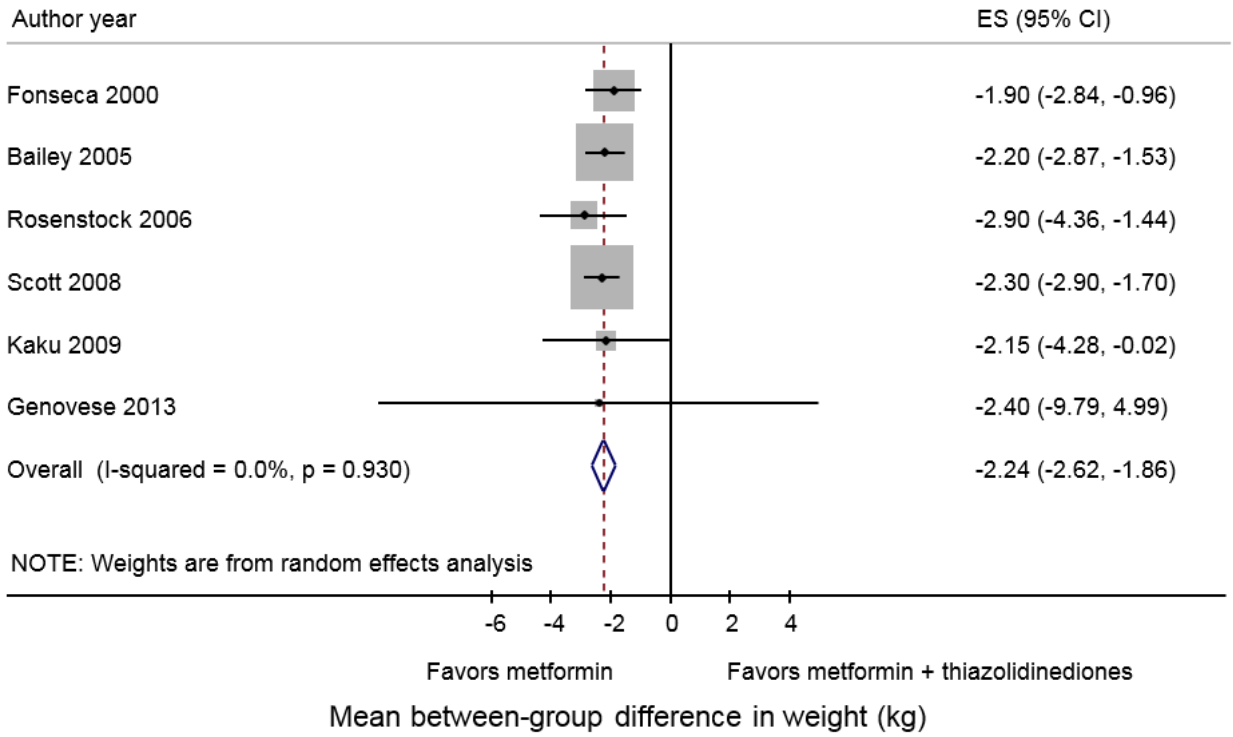
Two RCTs compared a DPP-4 inhibitor (sitagliptin) with a GLP-1 receptor agonist (exenatide or liraglutide), with both favoring the GLP-1 receptor agonist. The first double-blind RCT compared sitagliptin at 100 mg daily with exenatide 2 mg weekly for 26 weeks, with greater weight reduction in the exenatide arm (calculated mean between-group difference in weight of 1.2 kg; 95% CI, 0.5 kg to 1.9 kg).[73] A second open-label RCT, with 40 subjects and lasting 24 weeks, compared sitagliptin at 50 mg daily with liraglutide titrated to 0.9 mg daily, with no significant difference in weight between groups (calculated mean between-group difference in weight of 1.5 kg; 95% CI, -24 kg to 27 kg).[115] (SOE: Low; GLP-1 receptor agonists favored)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

We combined six studies which directly compared metformin monotherapy with the combination of metformin plus a thiazolidinedione (mostly rosiglitazone), showing a pooled between-group difference in weight of -2.2 kg (95% CI, -2.6 kg to -1.9 kg) favoring metformin (Figure 22).[59, 117, 118, 120, 123, 125] No single study markedly affected the results, and there was no significant heterogeneity between studies. All six studies showed that the metformin arms had weight loss while the combination arms had weight gain. Four studies were excluded from the meta-analysis due to insufficient quantitative data to combine the studies[67, 116, 126] or due to study duration differences.[127] All four of these studies reported modest weight gain in the combination arms, which was consistent with the studies included in the meta-analysis.[67, 116, 126, 127] (SOE: High; Metformin favored)

Figure 22. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a thiazolidinedione

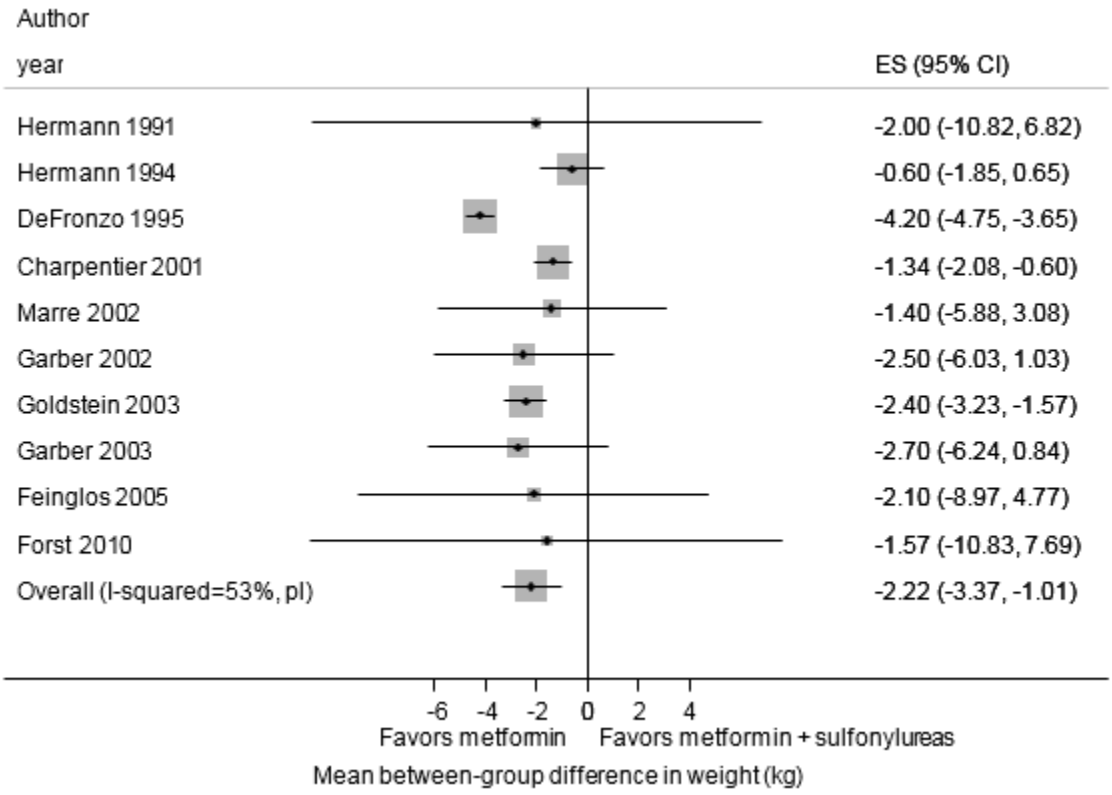


CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

Ten short RCTs compared metformin with the combination of metformin plus a sulfonylurea, favoring metformin monotherapy, with a pooled between-group difference of -2.2 kg (95% CI, -3.4 kg to -1.0 kg) (Figure 23).[128-130, 132-137, 139] No single study markedly influenced the results. While heterogeneity existed, all studies favored the metformin arm over the combination arm, with minimal between-group differences among the studies. In meta-regression, baseline weight was identified as a significant source of heterogeneity; dosing differences, double blinding, study duration, and appropriate randomization were not identified as significant. Baseline weight explained 55 percent of the between-study heterogeneity (adjusted r-squared = 55%). We present the stratified meta-analyses in Table 9. One 104-week study with 30 percent to 40 percent loss to followup, depending on the treatment arm, was excluded from the meta-analysis due to its long duration.[141] The mean between-group difference in weight favored the metformin monotherapy arm, non-significantly, by 2.2 kg.[141] (SOE: High; Metformin favored)

Figure 23. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a sulfonylurea



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

Table 9. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a sulfonylurea, stratified by baseline weight

Variables	N of Studies	WMD (95% CI)	I^2	Summary
Baseline weight ≥ 90 kg*	5	-3.2 kg (-4.6 kg to -1.6 kg)	56%	Favors metformin
Baseline weight < 90 kg	5	-1.2 kg (-1.8 kg to -0.6 kg)	0%	Favors metformin

CI = confidence interval; kg = kilogram; WMD = weighted mean difference
* Analysis was calculated using a profile likelihood estimate.

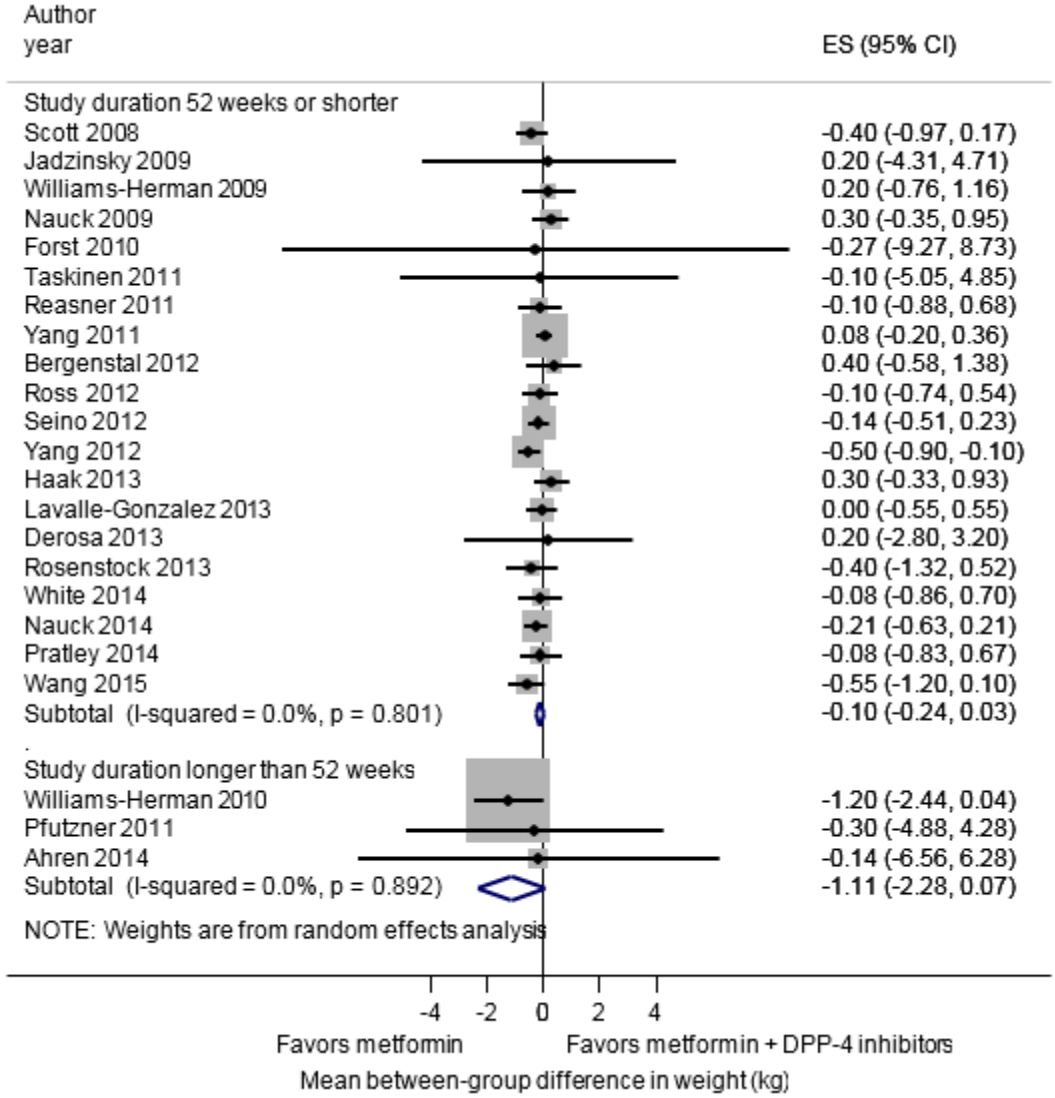
Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

We combined twenty RCTs, each lasting 1 year or less, comparing metformin with the combination of metformin plus a DPP-4 inhibitor (pooled between-group difference of -0.1 kg; 95% CI, -0.24 kg to 0.03 kg) (Figure 24).[51, 81, 83, 84, 86, 118, 139, 145, 146, 148, 150-155, 157-160] No substantial heterogeneity was found. In a standard sensitivity analysis, the removal of the study by Lavalle-Gonzalez and colleagues significantly changed the pooled estimate to significantly favor metformin monotherapy slightly. However, there were no clear qualitative differences to prompt removal of this study. Two studies[147, 162] were excluded from the meta-analysis due to higher doses of metformin in the monotherapy arms by 500 to 1000 mg daily compared with the combination arms. In these two studies, greater weight loss was seen in the metformin

monotherapy arms.[147, 162] Six studies with similar results to the other studies were excluded from the short duration meta-analysis due to absence of data needed to quantitatively combine the studies.[126, 143, 144, 149, 156, 163]

We also pooled three longer studies (two of which were extension studies), each lasting 76 to 104 weeks and with greater than 20 percent losses to followup, that compared metformin with a metformin plus a DPP-4 inhibitor. Consistent with the short studies, these trials showed no significant difference in weight (pooled between-group difference in weight of 1.1 kg; 95% CI, -2.3 kg to 0.07 kg) (Figure 24).[85, 87, 141] No single study markedly influenced the results, and no substantial heterogeneity was found. (SOE: Moderate; Neither favored for studies 52 weeks or shorter) (SOE: Low; Neither drug favored for studies 1.5 to 2 years)

Figure 24. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration



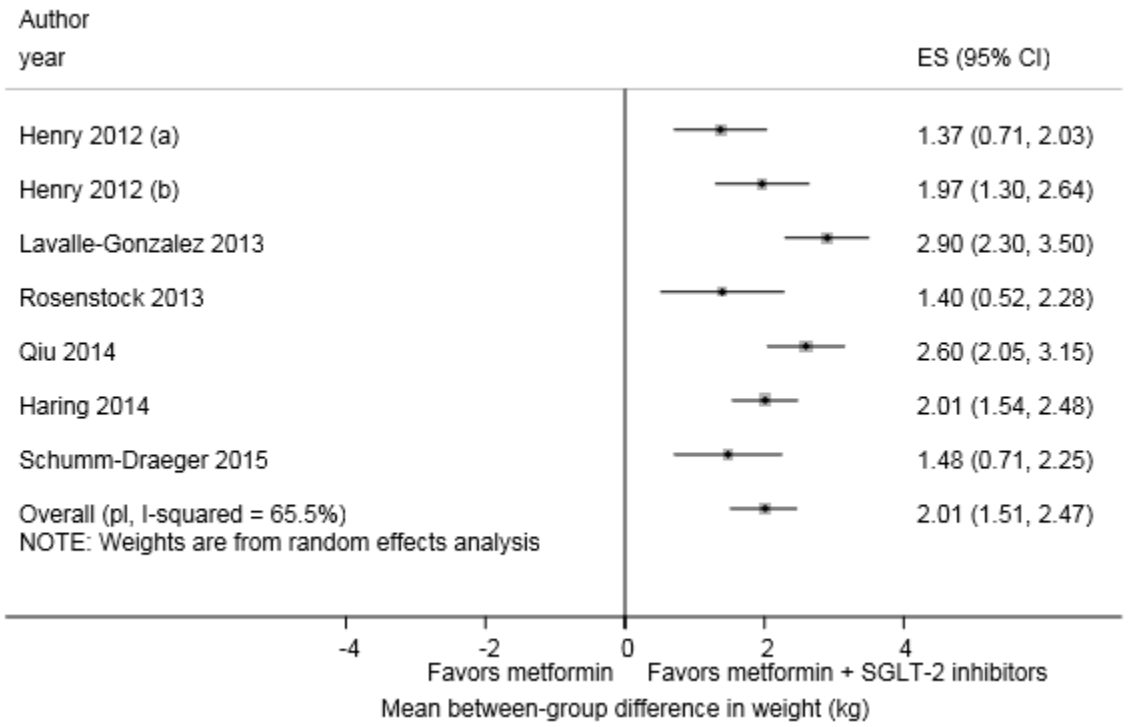
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Seven RCTs (reported in six articles), each lasting 26 weeks or less, compared metformin alone with the combination of metformin plus an SGLT-2 inhibitor, with greater weight reductions in the combination arm (pooled between-group difference in weight of 2.0 kg; 95% CI, 1.5 kg to 2.5 kg) (Figure 25).[88, 153, 158, 165, 166, 168] No single study markedly influenced the results. There was substantial statistical heterogeneity among the studies, yet the individual between-group differences were similar among the studies. One additional short RCT was excluded, since it only reported percent change in weight, but it also favored the combination of metformin plus an SGLT-2 inhibitor.[156] Two 102-week RCTs were excluded from the meta-analysis due to study duration differences.[169, 170] These longer RCTs, with 20 percent to 40 percent losses to followup, also significantly favored the combination of metformin plus an SGLT-2 inhibitor, with the range in between-group differences in weight of 2.4 kg to 3.1 kg. (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 25. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram; pl = profile likelihood estimate; SGLT-2 = sodium-glucose co-transporter-2

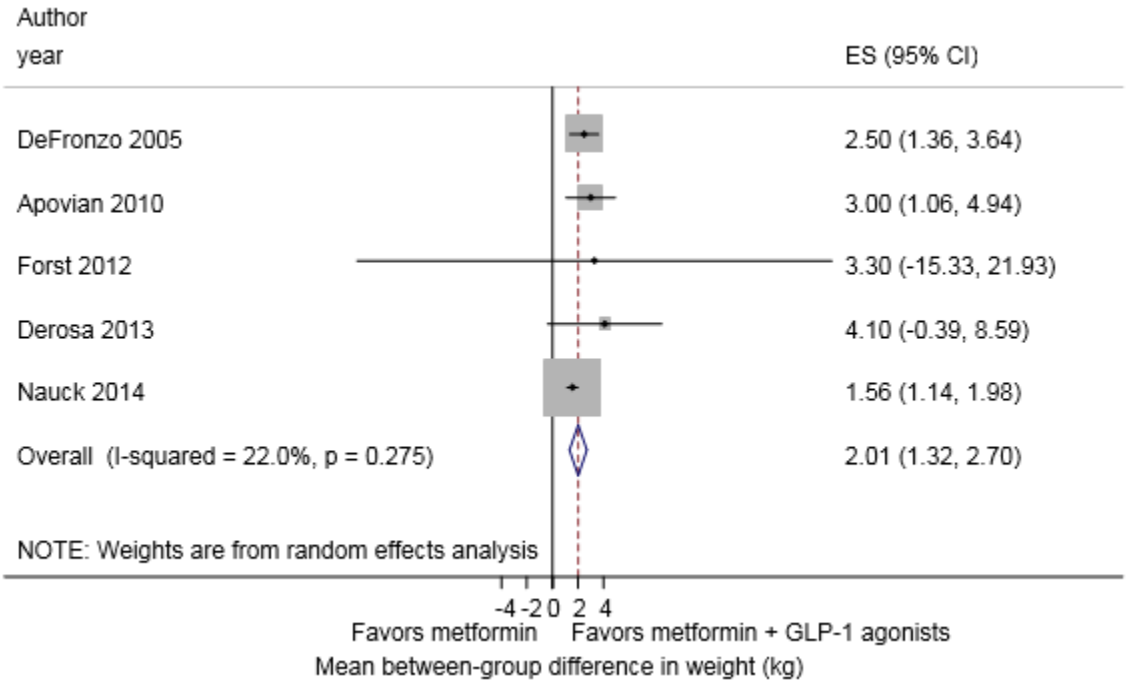
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

Metformin Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Five RCTs, each lasting 48 weeks or less, compared metformin with the combination of metformin plus a GLP-1 receptor agonist, with all five studies showing greater weight reduction in the combination metformin plus GLP-1 receptor agonist arm (pooled between-group

difference of 2.0 kg; 95% CI, 1.3 kg to 2.7 kg) (Figure 26).[159, 171-174] No one study strongly influenced the pooled results, and no substantial heterogeneity was identified. The one short study which had two dosing arms of the combination showed a smaller between-group difference in weight when comparing the metformin monotherapy arm to the lower dose combination arm versus the higher dose combination arm.[159] One 104-week RCT excluded from the meta-analysis showed a non-significant greater weight reduction in the combination arm of 0.2 kg, but had 30 percent to 40 percent losses to followup, depending on the treatment arm.[141] (SOE: Moderate; Combination of metformin plus a GLP-1 receptor agonist favored)

Figure 26. Pooled mean between-group difference in weight comparing metformin with a combination of metformin plus a GLP-1 receptor agonist



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); GLP-1 = glucagon-like peptide-1; kg = kilogram
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

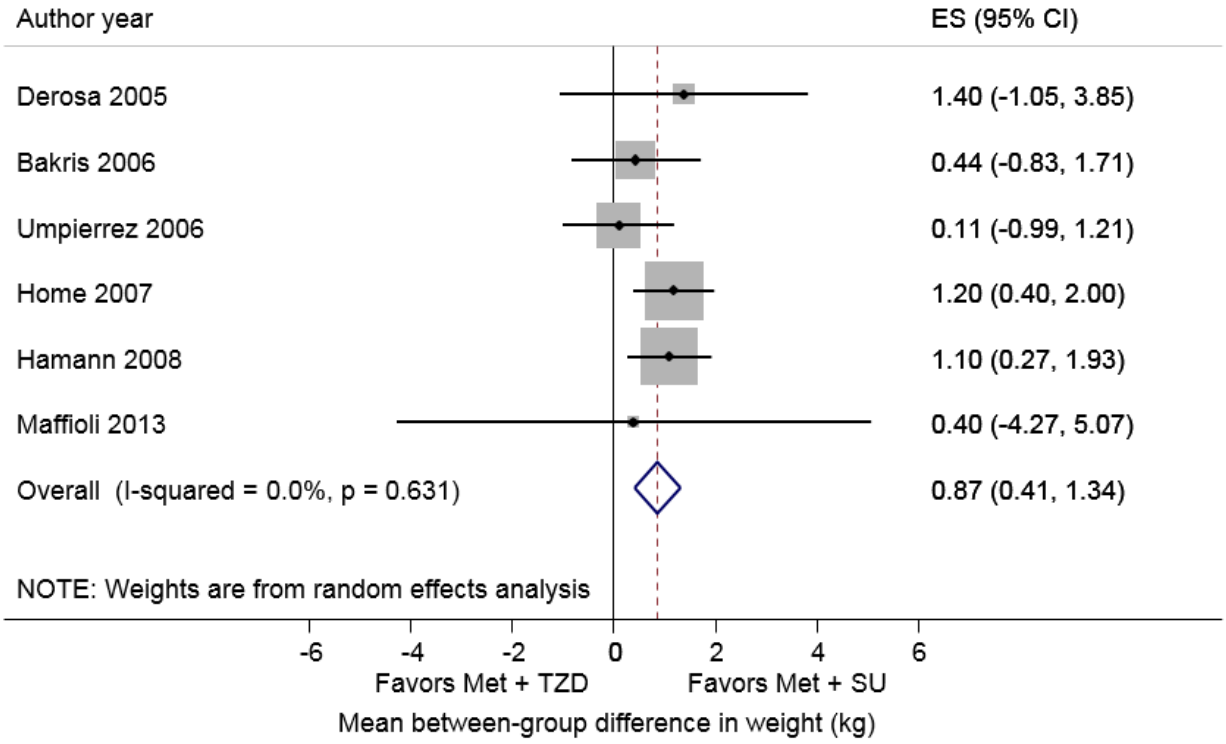
We combined six comparably-dosed studies, each lasting less than one year, that directly compared metformin plus a thiazolidinedione with metformin plus a sulfonylurea.[175-178, 181, 218] The pooled mean between-group difference favored the combination of metformin plus sulfonylurea by 0.9 kg (95% CI, 0.4 kg to 1.3 kg) (Figure 27). No one study markedly influenced the results, and no substantial heterogeneity was found.

In the meta-analysis, we included the short-term results from the large RECORD study.[176] The RECORD study was a multicenter, open-label RCT evaluating 4,447 patients with type 2

diabetes and uncontrolled glycemia already on metformin or sulfonylurea monotherapy, with less than 20 percent losses to followup.[49, 176] Body weight increased significantly with rosiglitazone plus metformin compared with sulfonylurea plus metformin, with a mean between-group difference of 1.2 kg (95% CI, 0.4 kg to 2.0 kg) after 18 months.[176] The mean between-group difference increased to 3.8 kg after 5 years of followup.[49]

We excluded three short RCTs from the meta-analysis, since the dosing was not comparable with the other studies.[180, 184, 185] One[180] used a lower dose of metformin in the metformin plus sulfonylurea arm compared with a higher dose of metformin in the metformin plus thiazolidinedione arm. The two other short RCTs used low doses of a sulfonylurea in the metformin plus sulfonylurea arm.[184, 185] As a sensitivity analysis, we included these three RCTs in the meta-analysis and noted no meaningful change in results (pooled mean between-group difference in weight of 0.8 kg).[180, 184, 185] (SOE: Moderate; Combination of metformin plus a sulfonylurea favored)

Figure 27. Pooled mean between-group difference in weight comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); Met = metformin; kg = kilogram; SU = sulfonylurea; TZD = thiazolidinedione

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

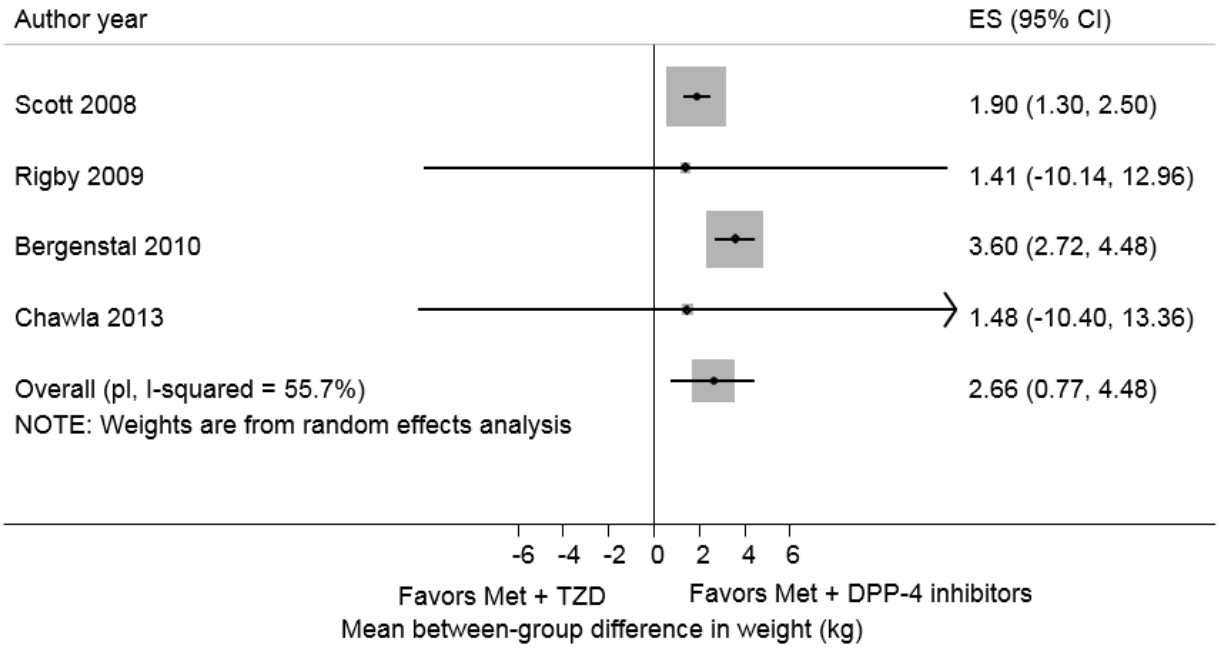
Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Four short-duration RCTs compared metformin plus a thiazolidinedione with the combination of metformin plus a DPP-4 inhibitor, favoring the combination of metformin plus a DPP-4 inhibitor (pooled mean between-group difference of 2.7 kg; 95% CI, 0.8 kg to 4.5 kg)

(Figure 28).[118, 186-188] The patients in the metformin plus DPP-4 inhibitor arms had a mean weight loss, and the patients in the metformin plus thiazolidinedione arms had a mean weight gain. No single study markedly influenced the results. Substantial heterogeneity was identified; however, all four studies favored the metformin plus DPP-4 inhibitor arms by 1.4 to 3.6 kg. We were unable to quantitatively explore heterogeneity due to the small numbers of studies, but there were differences in baseline weight and drug types.

One additional short-duration RCT comparing metformin plus pioglitazone with metformin plus alogliptin was excluded from the meta-analysis, since it did not have sufficient quantitative data.[126] The study reported a decrease in weight of 0.7 kg in the metformin plus alogliptin arms but only stated qualitatively that there was an increase in weight in the metformin plus pioglitazone arm, consistent with the direction of weight change in the other four studies.[126] (SOE: Moderate; Combination of metformin plus a DPP-4 inhibitor favored)

Figure 28. Pooled mean between-group difference in weight comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); Met = metformin; kg = kilogram; pl = profile likelihood estimate; TZD = thiazolidinedione
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

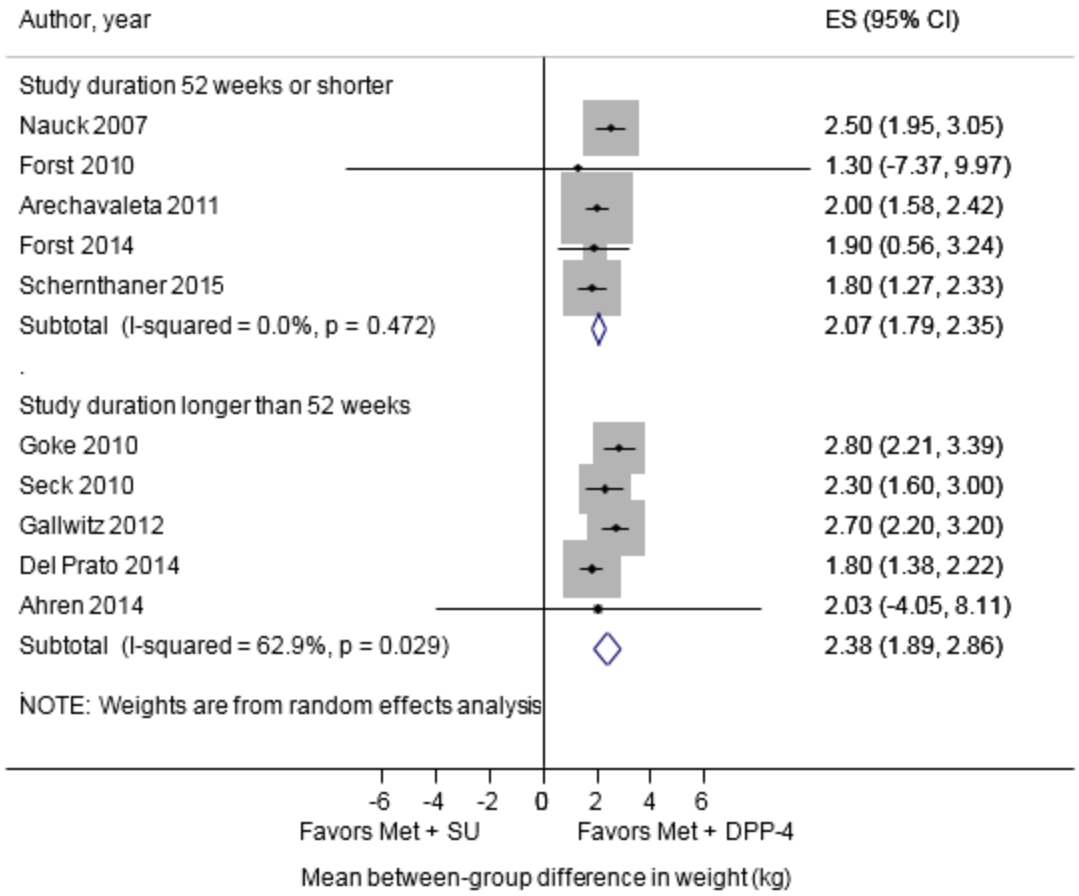
Two short, comparably-dosed RCTs compared metformin plus thiazolidinediones (pioglitazone or rosiglitazone) with metformin plus a GLP-1 receptor agonist (exenatide).[188, 189] Both studies significantly favored the combination of metformin plus a GLP-1 receptor agonist (range in mean between-group differences in weight, 2.7 kg to 5.1 kg). Both studies had weight gain in the metformin plus thiazolidinedione arms and weight loss in the metformin plus GLP-1

receptor agonist arms. (SOE: Moderate; Combination of metformin plus a GLP-1 receptor agonist favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Nine RCTS (reported in ten articles) compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a DPP-4 inhibitor.[139, 141, 190-197] Both the shorter (1 year or less) and longer (2-year) studies favored the metformin plus DPP-4 inhibitor arms (Figure 29). The metformin plus sulfonylurea arms all had weight gain, and the metformin plus DPP-4 inhibitor arms all had weight loss or weight maintenance. The five RCTs, each lasting 1 year or less, had a pooled between-group difference in weight of 2.1 kg (95% CI, 1.8 kg to 2.3 kg)[139, 190-193] and the five RCTs, each lasting 2 years and with greater than 30 percent losses to followup, had a pooled between-group difference of 2.4 kg (95% CI, 1.9 kg to 2.9 kg).[141, 194-197] No single study markedly influenced the results. While substantial statistical heterogeneity was identified in the meta-analysis of the longer studies, all studies favored the combination with similar effects. (SOE: High; Combination of metformin plus a DPP-4 inhibitor favored)

Figure 29. Pooled mean between-group difference in weight comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration



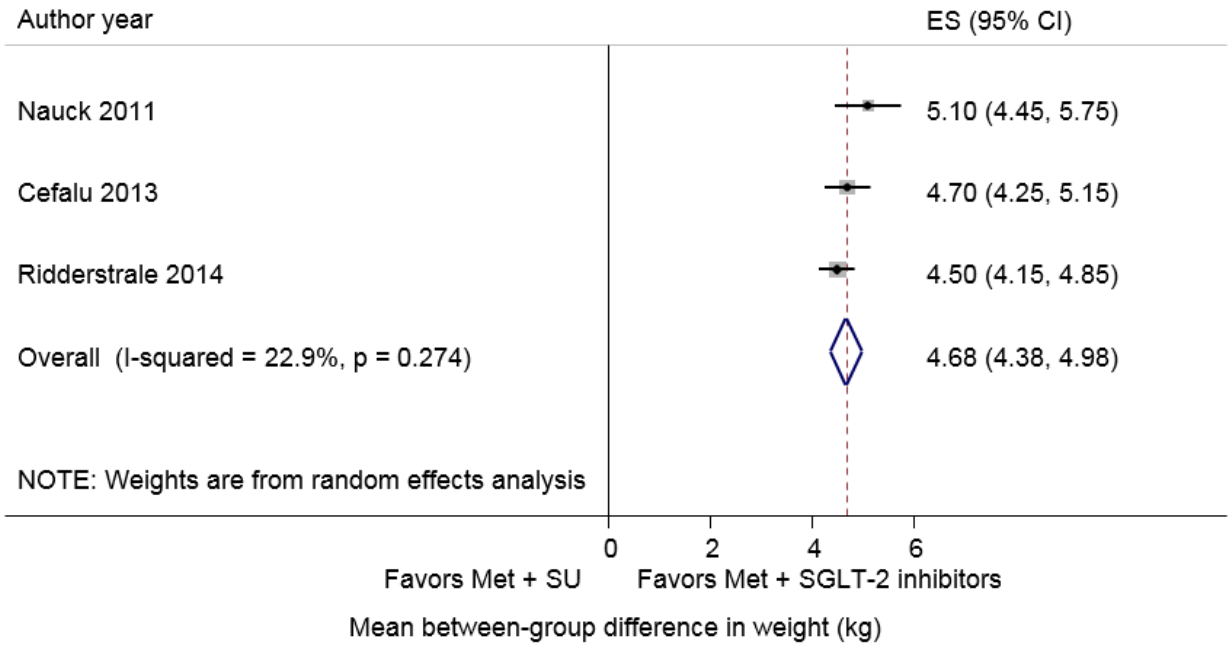
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram; Met = metformin; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Three RCTs, each lasting 52 to 104 weeks, compared the combination of metformin plus a sulfonylurea (glimepiride or glipizide) with the combination of metformin plus an SGLT-2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin).[198-200] The combination of metformin plus an SGLT-2 inhibitor was strongly favored (pooled mean between-group difference in weight of 4.7 kg; 95% CI, 4.4 kg to 5.0 kg) (Figure 30). No single study markedly influenced the results, and no substantial heterogeneity was found. One of the RCTs, which had a lower and higher dose metformin plus canagliflozin arm, demonstrated a small dose-response effect in weight reduction, with a smaller mean between-group difference in weight in the lower dose arm of 4.4 kg versus 4.7 kg in the higher dose arm.[198] Two extension studies, lasting 2 years[201] and 4 years[54] with 30 percent to 60 percent losses to followup, were also identified, showing consistent findings to the shorter studies (calculated mean between-group differences in weight of 4.4 kg

favoring the combination of metformin plus an SGLT-2 inhibitor). (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 30. Pooled mean between-group difference in weight comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram; Met = metformin; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Four RCTs, three lasting less than 1 year and one lasting 2 years, compared metformin plus sulfonylurea with metformin plus a GLP-1 receptor agonist.[141, 203-205] These favored the combination of metformin and GLP-1 receptor agonist (range in mean between-group differences of 2.4 kg to 12.3 kg). All four RCTs showed weight loss with the combination of metformin and GLP-1 receptor agonists and weight gain with the combination of metformin and sulfonylureas. We did not combine these studies in a meta-analysis due to differences in drug dosing, drug type, and study duration.

One RCT compared metformin plus a sulfonylurea with three different dosing arms of metformin plus liraglutide. The arms with lower doses of liraglutide had smaller between-group differences in weight relative to the higher dose arm.[204] (SOE: Moderate; Combination of metformin plus a GLP-1 receptor agonist favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a Basal Insulin

One small, open-label RCT, lasting 48 weeks, compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a basal insulin, favoring metformin plus sulfonylurea (mean between-group difference in weight of -1.7 kg; 95% CI, -3.1 kg to -0.3

kg).[206] Patients were kept on their prior metformin doses and were randomized to uptitration of glimepiride (mean daily dose of 4 mg) versus uptitration of insulin glargine (mean daily dose of 23 units) until a fasting plasma glucose target was reached. Individuals in the metformin plus sulfonylurea arm had no change in weight, and those in the metformin plus insulin glargine arm gained weight. (SOE: Low; Combination of metformin plus a sulfonylurea favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a Premixed Insulin

Two short RCTs compared metformin plus glibenclamide with the combination of metformin plus a premixed insulin analogue: insulin aspart 70/30 in one study and insulin lispro 75/25 in the other study.[207, 208] Both studies favored the metformin plus sulfonylurea arms (range in between-group differences of -0.7 kg to -0.5 kg). One of the two studies showed a statistically significant difference. There was not a mean decrease in weight in any of the study arms.

Of note, if we combine the three studies comparing metformin plus sulfonylurea with metformin plus a premixed or basal insulin (adding in the study described in the prior comparison), metformin plus sulfonylurea is favored, with a weighted mean between-group difference in weight of -0.67 kg (95% CI, -0.83 kg to -0.51 kg). No single study influenced the results and no substantial heterogeneity was identified. Since premixed and basal insulins may have similar effects on weight, it may be reasonable to combine these categories. (SOE: Low; Combination of metformin plus a sulfonylurea favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Five RCTs compared metformin plus a DPP-4 inhibitor with the combination of metformin plus an SGLT-2 inhibitor (range in mean between-group differences in weight of 1.8 kg to 3.6 kg).[90, 153, 156, 158, 209] All five studies significantly favored the combination of metformin plus an SGLT-2 inhibitor. We did not combine these studies due to differences in study duration and reporting of the outcome. The first 12-week RCT reported a mean percent change in weight of -0.6 percent in the metformin plus DPP-4 arm versus -3.4 percent in the metformin plus SGLT-2 inhibitor arm.[156] The second 12-week RCT reported a mean between-group difference in weight of 1.8 kg (95% CI, 1.9 kg to 2.7 kg).[153] The third 24-week RCT had a calculated mean between-group difference in weight of 2.4 kg (95% CI, 1.7 kg to 3.1 kg), favoring the metformin plus dapagliflozin arm over the metformin plus alogliptin arm.[209] The two longer RCTs, lasting 52 to 90 weeks and with less than 20 percent losses to follow-up, reported mean between-group differences of 2.9 kg and 3.6 kg, favoring the metformin plus SGLT-2 inhibitor arms.[90, 158] Two of the three studies with lower dose and higher dose combinations of metformin plus SGLT-2 inhibitor arm demonstrated a dose-response effect in weight reduction, with smaller between-group differences in the lower dose arms and larger between-group differences in the higher dose arms.[90, 158] (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

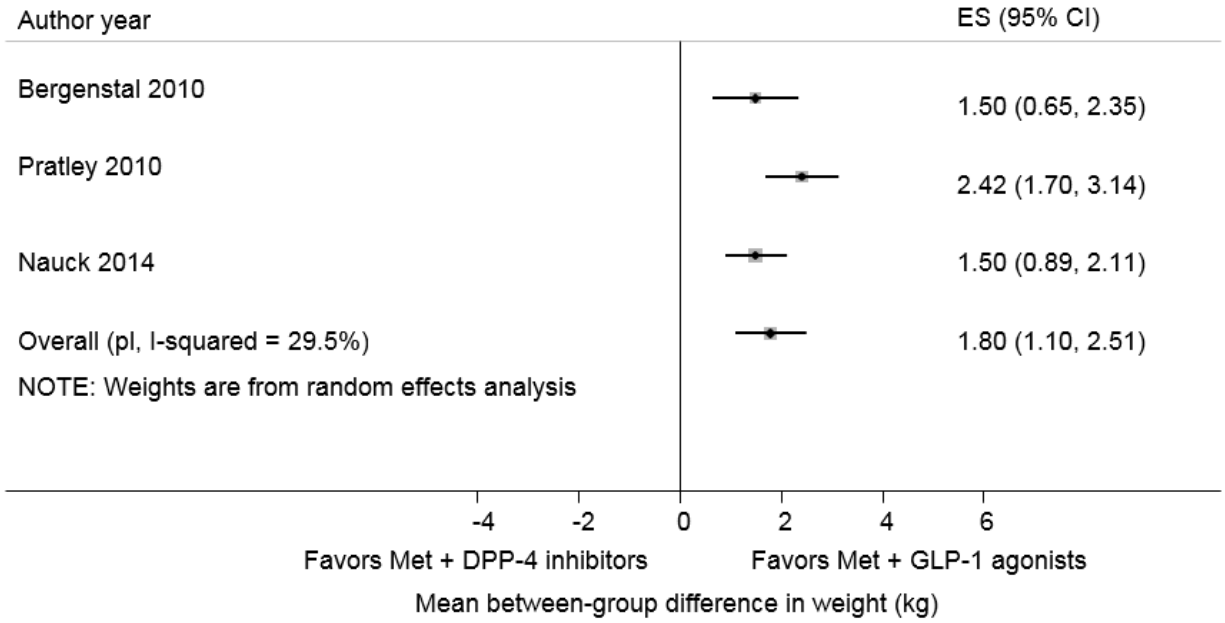
We combined three short RCTs comparing the combination of metformin plus a DPP-4 inhibitor with the combination of metformin plus a GLP-1 receptor agonist.[159, 188, 210] All three studies significantly favored the combination of metformin plus a GLP-1 receptor agonist (pooled mean between-group difference, 1.8 kg; 95% CI, 1.1 kg to 2.5 kg) (Figure 31).

Individuals in both arms lost weight but the metformin plus GLP-1 receptor agonist decreased weight more than the metformin plus DPP-4 treatment. No single study markedly influenced the results. Moderate heterogeneity was identified, although studies and point estimates were relatively similar.

The two studies with both low dose and high dose arms of the GLP-1 receptor agonist showed smaller between-group differences in weight for the lower dose arms (between-group differences for lower dose arms of 1.9 kg and 1.1 kg compared with the higher dose arm of 2.5 kg and 1.5 kg).[159, 210]

One 104-week RCT, with 30 percent to 40 percent losses to followup depending on the treatment arm, reported a non-significant between-group difference in weight of 0.4 kg (95% CI, -4.7 kg to 5.4 kg).[141] (SOE: Moderate; Combination of metformin plus a GLP-1 receptor agonist favored)

Figure 31. Pooled mean between-group difference in weight comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 receptor agonist



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); GLP-1 = glucagon-like peptide-1; kg = kilogram; Met = metformin; pl = profile likelihood estimate
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a Basal Insulin

One 24-week RCT compared metformin plus sitagliptin (100 mg daily) with metformin plus insulin glargine titrated to 0.5 units per kg. The RCT significantly favored the metformin plus DPP-4 arm (mean between-group difference in weight of -1.5 kg; 95% CI, -2.1 kg to -0.9 kg).[211] The metformin plus DPP-4 arm decreased weight, and the metformin plus insulin glargine arm increased weight. (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored)

Combination of Metformin Plus a GLP-1 Receptor Agonist Versus a Combination of Metformin Plus a Basal Insulin

One 26-week, comparably-dosed RCT compared metformin plus exenatide (2 mg weekly) with metformin plus glargine insulin (titrated based on blood sugars). This RCT showed a mean between-group difference of -4.7 kg, favoring the combination of metformin plus a GLP-1 receptor agonist.[212] (SOE: Insufficient)

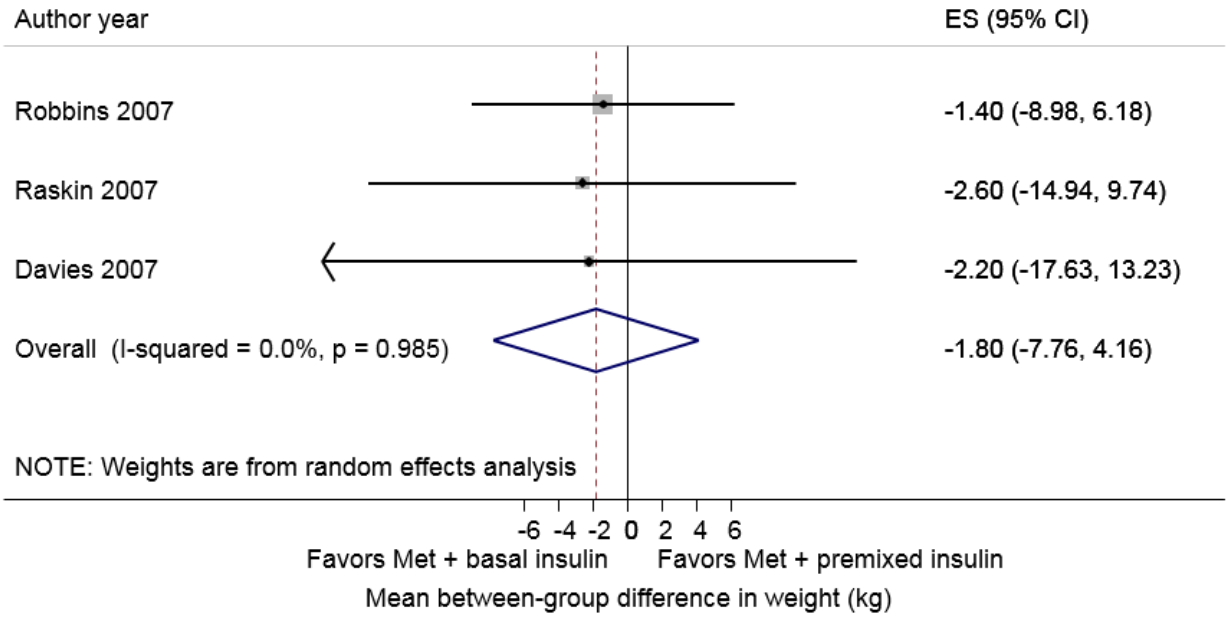
Combination of Metformin Plus a GLP-1 Receptor Agonist Versus a Combination of Metformin Plus a Premixed Insulin

One moderately-sized RCT, lasting 26 weeks, compared the combination of metformin plus exenatide (titrated to 20 micrograms) with the combination of metformin plus premixed insulin (titrated to glucose target, mean dose 28 units).[213] The RCT significantly favored metformin plus exenatide (mean between-group difference in weight of -5.1 kg; 95% CI, -5.7 kg to -4.5 kg). The metformin plus GLP-1 receptor agonist arm decreased weight, and the metformin plus premixed insulin arm increased weight. (SOE: Low; Combination of metformin plus a GLP-1 receptor agonist favored)

Combination of Metformin Plus a Basal Insulin Versus a Combination of Metformin Plus a Premixed Insulin

Three RCTs directly compared the combination of metformin plus basal insulin with the combination of metformin plus premixed insulin, showing no between-group differences in weight (pooled mean between-group difference of -1.8 kg; 95% CI, -7.8 kg to 4.2 kg) (Figure 32).[214-216] No single study strongly influenced the results, and no substantial heterogeneity was found. (SOE: Low; Neither treatment favored)

Figure 32. Pooled mean between-group difference in weight comparing a combination of metformin plus a basal insulin with a combination of metformin plus a premixed insulin



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); kg = kilogram; Met = metformin

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Strength of Evidence for Weight

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 10, Table 11, and Table 12 and summarized in the Key Points. All studies were RCTs. Study limitations for most comparisons were low or medium, with only two comparisons having high study limitations due to lack of blinding, lack of description of withdrawals and dropouts, and very high losses to followup. Where quality influences results, we describe that under the appropriate comparisons. In general, we did not find strong differences in outcomes in the lower-quality versus higher-quality studies. We did not find any evidence of publication bias in any of the comparisons for weight which would have impacted the results. We also did not find any evidence of publication bias or reporting bias in the grey literature review. Eleven studies did not report a measure of dispersion; however, addition of these studies would not have importantly changed our conclusions or the strength of evidence assessment. We considered weight a direct outcome, since patients care about weight independent of its cardiovascular effects. Several of the comparisons were downgraded due to imprecision. The comparisons were considered imprecise mainly due to the small and not clinically relevant between-group differences in weight of 2 pounds or less.

Table 10. Strength of evidence domains for monotherapy comparisons in terms of weight among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. TZD‡	NA	NA	NA	NA	NA	NA	High	Metformin favored; -2.6 kg (-4.1 to -1.2 kg)
Metformin vs. SU‡	NA	NA	NA	NA	NA	NA	High	Metformin favored; -2.7 kg (-3.5 to -1.9 kg)
Metformin vs. DPP-4 inhibitors	6 (6700)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin favored; -1.3 kg (-1.6 to -1.0 kg)
Metformin vs. SGLT-2 inhibitors	3 (1903)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	SGLT-2 inhibitors favored; range of between-group differences, -1.3 to -1.4 kg
Metformin vs. GLP-1 receptor agonists	3 (1089)	Low	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
TZD vs. SU	9 (6766)	Medium	Inconsistent	Direct	Precise	Undetected	Moderate	SU favored; 1.2 kg (0.6 to 1.8 kg)
TZD vs. DPP-4 inhibitors	2 (1475)	Low	Consistent	Direct	Precise	Undetected	Moderate	DPP-4 inhibitors favored; range in between-group differences, 2.3 to 2.5 kg
TZD vs. GLP-1 receptor agonists	2 (1048)	Low	Consistent	Direct	Precise	Undetected	Moderate	GLP-1 receptor agonists favored; between-group differences for both studies, 3.5 kg
SU vs. DPP-4 inhibitors	3 (1271)	Low	Consistent	Direct	Imprecise	Undetected	Low	DPP-4 inhibitors favored
SU vs. GLP-1 receptor agonists	4 (1157)	Medium	Consistent	Direct	Precise	Undetected	Moderate	GLP-1 receptor agonists favored; 2.3 (1.2 to 3.3 kg)
DPP-4 inhibitors vs. SGLT-2 inhibitors	1 (899)	Low	Unknown	Direct	Precise	Undetected	Moderate	SGLT-2 inhibitors favored; between-group difference, 2.5 to 2.7 kg
DPP-4 inhibitors vs. GLP-1 receptor agonists	2 (860)	Low	Consistent	Direct	Imprecise	Undetected	Low	GLP-1 receptor agonists favored

DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; TZD = thiazolidinedione

* Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.
‡ We did not re-evaluate weight for the comparisons of metformin with thiazolidinediones and metformin with sulfonylureas because we previously rated these comparisons as having high strength of evidence.[16]

Table 11. Strength of evidence domains for metformin versus metformin-based combination comparisons in terms of weight among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + TZD	10 (5102)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin favored; -2.2 kg (-2.6 to -1.9 kg)
Metformin vs. metformin + SU	11 (3692)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin favored; -2.2 kg (-3.4 to -1.0 kg)
Metformin vs. metformin + DPP-4 inhibitors (studies 1 year or shorter)	28 (16,837)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Neither treatment favored; -0.1 kg (-0.2 to 0.03 kg)
Metformin vs. metformin + DPP-4 inhibitors (studies 1.5 to 2 years)	3 (3446)	High	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. metformin + SGLT-2 inhibitors	10 (5978)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitors favored; 2.0 kg (1.5 to 2.5 kg)
Metformin vs. metformin + GLP-1 receptor agonists	6 (2882)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 receptor agonists favored; 2.0 kg (1.3 to 2.7 kg)

DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.

‡ We did not re-evaluate weight for the comparisons of metformin with thiazolidinediones and metformin with sulfonylureas because we previously rated these comparisons as having high strength of evidence.[16]

Table 12. Strength of evidence domains for metformin-based combination comparisons in terms of weight among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + TZD vs. metformin + SU	9 (2928)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + SU favored; 0.9 kg (0.4 to 1.3 kg)
Metformin + TZD vs. metformin + DPP-4 inhibitors	5 (2413)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin + DPP-4 inhibitors favored; 2.7 kg (0.8 to 4.5 kg)
Metformin + TZD vs. metformin + GLP-1 receptor agonists	2 (604)	Low	Consistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 receptor agonists favored; range in mean between-group differences, 2.7 to 5.1 kg
Metformin + SU vs. metformin + DPP-4 inhibitors (studies ≤ 1 year)	5 (3300)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + DPP-4 inhibitors favored; 2.1 kg (1.8 to 2.3 kg)
Metformin + SU vs. metformin + DPP-4 inhibitors (2-year studies)	5 (7270)	High	Consistent	Direct	Precise	Undetected	Low	Metformin + DPP-4 inhibitors favored
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration studies)	3 (3815)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitors favored; 4.7 kg (4.4 to 5.0 kg)
Metformin + SU vs. metformin + GLP-1 receptor agonists	4 (3304)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin + GLP-1 receptor agonists favored; range in between-group differences 2.4 kg to 12.3 kg
Metformin + SU vs. metformin + basal insulin	1 (75)	Medium	Unknown	Direct	Precise	Undetected	Low**	Metformin + SU favored
Metformin + SU vs. metformin + premixed insulin	2 (819)	Medium	Consistent	Direct	Imprecise	Undetected	Low**	Metformin + SU favored

Table 12. Strength of evidence domains for metformin-based combination comparisons in terms of weight among adults with type 2 diabetes (continued)

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	5 (3423)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + SGLT-2 inhibitors favored; range in between-group differences 1.8 to 3.6 kg
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 receptor agonists	4 (3322)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 receptor agonists favored; 1.8 kg (1.1 to 2.5 kg)
Metformin + DPP-4 inhibitors vs. metformin + basal insulin	1 (515)	Medium	Unknown	Direct	Precise	Undetected	Low	Metformin + DPP-4 inhibitors favored
Metformin + GLP-1 receptor agonists vs. metformin + basal insulin	1 (321)	Medium	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine effect
Metformin + GLP-1 receptor agonists vs. metformin + premixed insulin	1 (363)	High	Unknown	Direct	Precise	Undetected	Low	Metformin + GLP-1 receptor agonists favored
Metformin + basal insulin vs. metformin + premixed insulin	3 (530)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored

DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.

** While each of these comparisons are rated low strength of evidence due to low numbers of studies, this would move to moderate if all three studies were combined in a row of metformin plus sulfonylurea versus metformin plus premixed or basal insulin, since all three studies were consistent, direct, precise, study limitations were medium, and reporting bias was undetected. Since premixed and basal insulins may have similar effects on weight, it may be reasonable to combine these categories.

Evidence for Systolic Blood Pressure

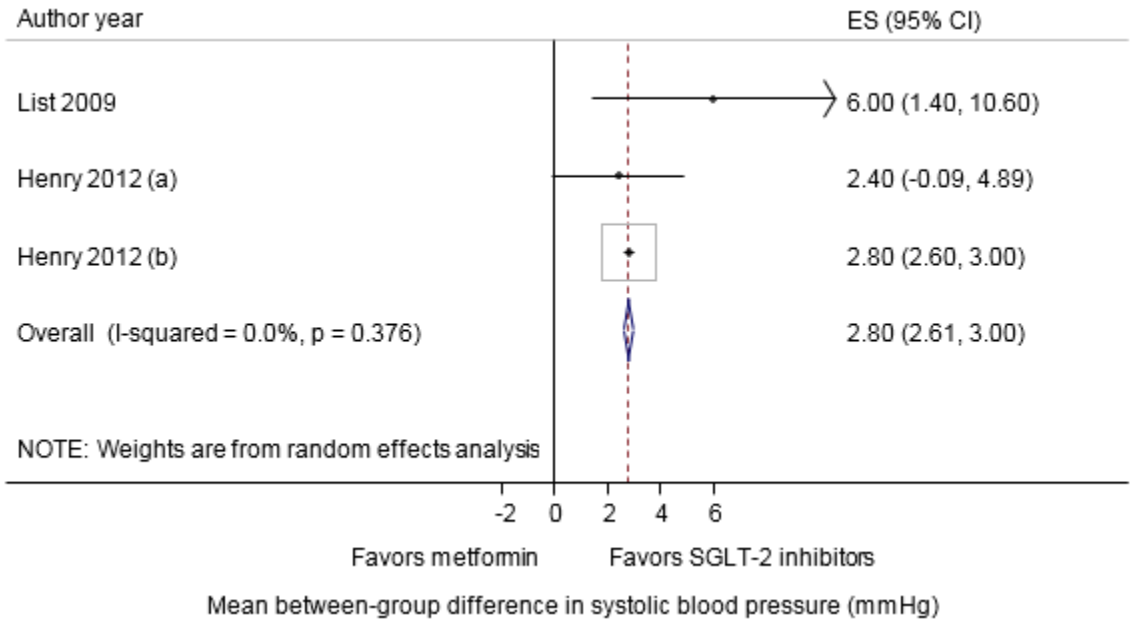
Monotherapy Comparisons

Metformin Versus SGLT-2 Inhibitors

We combined three short RCTs (reported in two articles) directly comparing metformin with a SGLT-2 inhibitor, favoring SGLT-2 inhibitors in systolic blood pressure reduction.[88, 89] Each study compared metformin with dapagliflozin,[88, 89] resulting in a pooled mean between-group difference in systolic blood pressure of 2.8 mmHg (95% CI, 2.6 mmHg to 3.0 mmHg) favoring SGLT-2 inhibitors over metformin (Figure 33). The metformin arms decreased mean systolic blood pressure by 0.4 mmHg to 1.8 mmHg, and the SGLT-2 inhibitors arms decreased mean systolic blood pressure by 4.0 mmHg to 6.4 mmHg. No single study markedly influenced the results, and there was no substantial heterogeneity.

We excluded one study from the meta-analysis given its length.[90] This trial was a randomized, open-label, 78-week extension of two shorter trials of empagliflozin. There was a non-significant between-group difference in systolic blood pressure of 3.7 mmHg (95% CI, -1.3 mmHg to 8.7 mmHg).[90] The metformin arm increased the mean systolic blood pressure by 2 mmHg, and empagliflozin (10 mg) increased mean systolic blood pressure by 0.1 mmHg, and empagliflozin (25 mg) decreased mean systolic blood pressure by 1.7 mmHg. (SOE: Moderate; SGLT-2 inhibitors favored)

Figure 33. Pooled mean between-group difference in systolic blood pressure comparing metformin with SGLT-2 inhibitors



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); mmHg = millimeters mercury; SGLT-2 = sodium-glucose co-transporter-2

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus GLP-1 Receptor Agonists

Two RCTs compared metformin with a GLP-1 receptor agonist, with inconclusive results.[73, 91] The first study was a 52-week RCT which compared two doses of dulaglutide with metformin; there was a 20 percent loss to followup in all arms. The RCT reported a non-significant between-group difference in systolic blood pressure of 1.7 mmHg (95% CI, -0.7 mmHg to 4.1 mmHg) with dulaglutide (0.75 mg weekly) and 0.9 mmHg (95% CI, -1.5 mmHg to 3.3 mmHg) with dulaglutide (1.5 mg weekly). The metformin arm increased mean systolic blood pressure by 1.0 mmHg, and the dulaglutide arms increased mean systolic blood pressure by 0.1 mmHg to 2.7 mmHg.[91] The second study was a 26-week RCT which showed a systolic blood pressure reduction of 1.3 mmHg with exenatide, but did not provide systolic blood pressure results for the metformin arm.[73] (SOE: Low; Neither drug favored)

Thiazolidinediones Versus GLP-1 Receptor Agonists

Two RCTs, ranging in duration from 26 to 48 weeks, compared pioglitazone with exenatide with inconsistent results.[73, 105] One 26-week RCT reported a non-significant between-group difference in systolic blood pressure of 0.4 mmHg (95% CI, -2.1 mmHg to 2.9 mmHg).[73] One 48-week RCT reported a significant between-group difference in systolic blood pressure of 3.0 mmHg (95% CI, 0.2 to 5.8 mmHg), favoring the GLP-1 arm.[105] (SOE: Insufficient)

Sulfonylureas Versus GLP-1 Receptor Agonists

One 104-week RCT compared glimepiride with liraglutide, and showed a non-significant between-group difference in systolic blood pressure of 0.9 mmHg (95% CI, -1.5 mmHg to 3.2 mmHg) with 1.2 mg of liraglutide and 1.9 mmHg (95% CI, -0.5 mmHg to 4.2 mmHg) with 1.8 mg of liraglutide.[113] Participants in all arms had a mean decrease in systolic blood pressure. There was high loss to followup of 50 percent to 60 percent, among all arms. (SOE: Low; Neither drug favored)

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

One double-blind, 24-week RCT compared sitagliptin (100 mg daily) to empagliflozin (10 mg and 25 mg daily). This RCT reported significant between-group differences in systolic blood pressure of 3.4 mmHg (95% CI, 1.2 mmHg to 5.7 mmHg) with 10mg of empagliflozin and 4.2 mmHg (95% CI, 2.0 mmHg to 6.5 mmHg) with 25mg of empagliflozin, favoring the SGLT-2 inhibitor over the DPP-4 inhibitor.[114] The DPP-4 inhibitor increased mean systolic blood pressure by 0.5 mmHg, and the empagliflozin decreased mean systolic blood pressure by 2.9 to 3.7 mmHg. (SOE: Low; SGLT-2 inhibitors favored)

DPP-4 Inhibitors Versus GLP-1 Receptor Agonists

Two RCTs, ranging in duration from 24 to 26 weeks, compared sitagliptin with a GLP-1 receptor agonist.[73, 115] One 26-week RCT, compared sitagliptin (100 mg daily) with exenatide (2 mg weekly), reporting a non-significant between-group difference in systolic blood pressure of 0.5 mmHg (95% CI -2.0 mmHg to 3.0 mmHg).[73] The DPP-4 inhibitor decreased mean systolic blood pressure by 1.8 mmHg, and the GLP-1 receptor agonist decreased mean systolic blood pressure by 1.3 mmHg. One 24-week RCT, comparing sitagliptin (50 mg daily) with liraglutide (titrated to 0.9 mg daily), had a small number of participants in each arm and a high withdrawal rate. They reported a non-significant between-group difference in systolic blood pressure of 6.9

mmHg (95% CI, -13.2 mmHg to 27.0 mmHg). This study reported high loss to followup (16 of 56 participants withdrew).[115] (SOE: Low; Neither drug favored)

Metformin Versus Metformin-Based Combination Comparisons

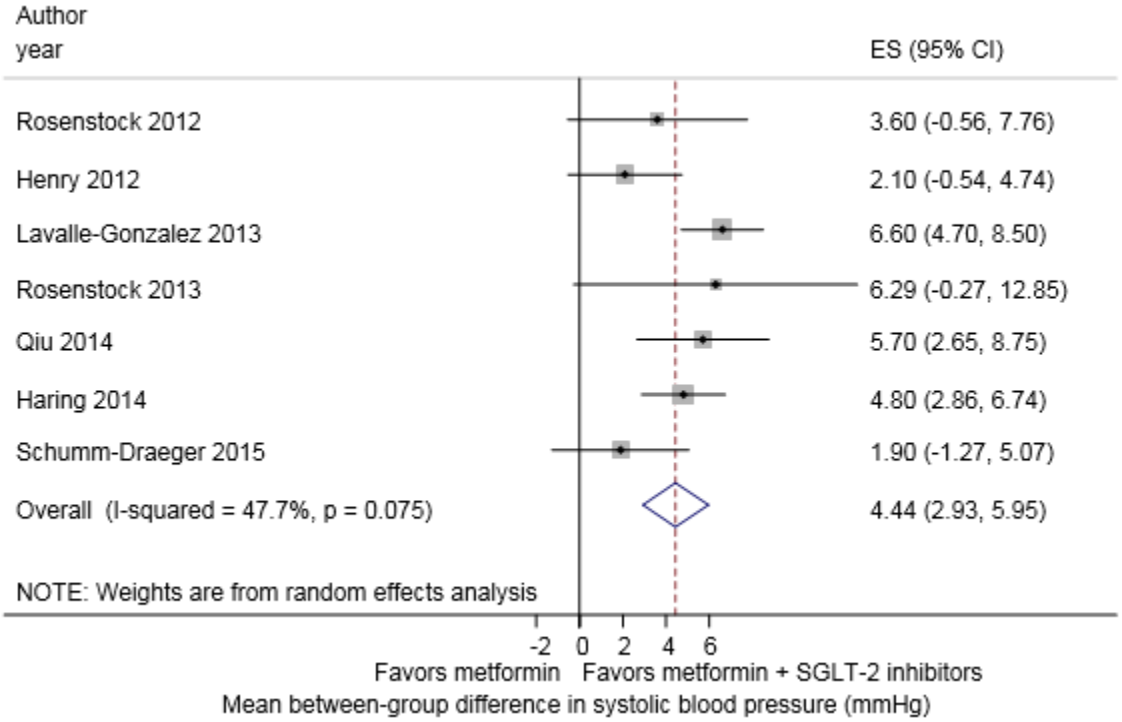
Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Seven RCTs (reported in six articles), each lasting less than one year, compared metformin to a combination of metformin and a SGLT-2 inhibitor. All studies favored the combination arm (pooled mean between-group difference in systolic blood pressure of 4.4 mmHg; 95% CI, 2.9 mmHg to 6.0 mmHg) (Figure 34).[88, 153, 156, 158, 165, 166, 168] The metformin arms did not have consistent effects on the change in mean systolic blood pressure, which ranged from -2.2 mmHg to 3.3 mmHg. However, the SGLT-2 inhibitor combination arms consistently decreased mean systolic blood pressure by 2.4 mmHg to 8.5 mmHg. No single study markedly influenced the results, and there was no substantial heterogeneity.

Two 102-week studies compared metformin with a combination of metformin and a SGLT-2 inhibitor and favored neither arm.[169, 170] The first study was a 102-week RCT which compared metformin (at least 1500 mg daily) with a metformin plus two different doses of dapagliflozin. This RCT showed a non-significant between-group difference in systolic blood pressure of 2.6 mmHg (95% CI, -1.6 mmHg to 6.8 mmHg) for the combination with 5mg of dapagliflozin and 1.8 mmHg (95% CI, -2.6 mmHg to 6.2 mmHg) for the combination with 10mg of dapagliflozin.[170] The metformin arm increased mean systolic blood pressure by 1.5 mmHg, and the dapagliflozin arms decreased mean systolic blood pressure by 0.3 mmHg to 1.1 mmHg. There was a high loss to followup in this study (47% in the metformin arm and 30% to 40% in the combination arms). The second study was a 102-week RCT with over 20 percent loss to followup in both arms. This second RCT compared metformin at the dosage prior to enrollment with metformin plus dapagliflozin (10 mg daily) and showed a non-significant between-group difference in systolic blood pressure of 2.4 mmHg (95% CI, -1.5 mmHg to 6.3 mmHg).[169] The metformin arm increased mean systolic blood pressure by 1.1 mmHg, and the metformin plus SGLT-2 inhibitor arm decreased mean systolic blood pressure by 1.3 mmHg.

One 24-week RCT was excluded from the meta-analysis due to differences in medication dosing for the SGLT-2 inhibitor arm. In this study, metformin was compared with metformin plus 5mg of dapagliflozin, showing a between-group difference in systolic blood pressure of 1.1 mmHg (95% CI, -1.4 mmHg to 3.6 mmHg) with both arms decreasing mean systolic blood pressure.[88] (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored for shorter studies; SOE: Low; Neither favored for longer studies)

Figure 34. Pooled mean between-group difference in systolic blood pressure comparing metformin with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); mmHg = millimeters mercury; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

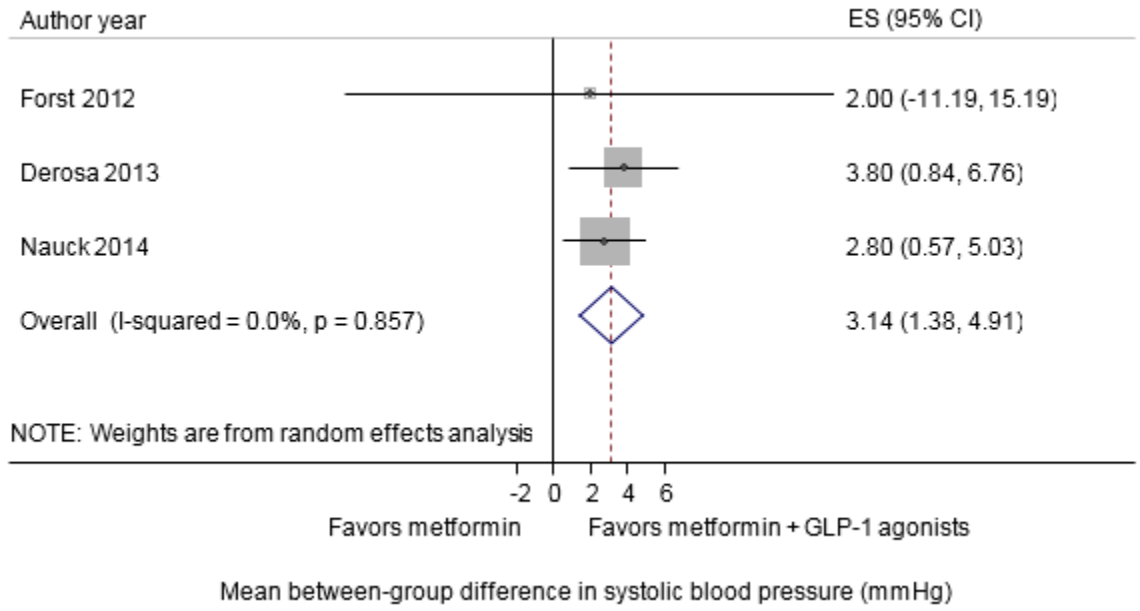
Metformin Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Three short RCTs, each lasting less than one year, compared metformin with a combination of metformin plus a GLP-1 receptor agonist. The pooled analysis showed a between-group difference in systolic blood pressure of 3.1 mmHg (95% CI, 1.4 mmHg to 4.9 mmHg), favoring the combination arm over the monotherapy arm (Figure 35).[159, 171, 172] These studies used different combinations of metformin plus a GLP-1 receptor agonist (liraglutide, dulaglutide, or exenatide). The metformin arms did not show consistent effects, with the mean change in systolic blood pressure ranging from -3.0 mmHg to 1.1 mmHg; the GLP-1 receptor agonist arms consistently decreased mean systolic blood pressure by 1.7 mmHg to 6.8 mmHg. No single study markedly influenced the results, and there was no substantial heterogeneity.

We excluded the 104-week RCT from the meta-analysis due to its long duration.[141] Consistent with the meta-analysis results, this study reported a significant between-group difference in systolic blood pressure of 3.2 mmHg (95% CI, 0.03 mmHg to 6.4 mmHg), favoring the combination arm.[141] The metformin arm increased mean systolic blood pressure by 2.2 mmHg, and the metformin plus albiglutide arm decreased mean systolic blood pressure by 1 mmHg. There were high losses to followup of 30 percent to 40 percent among both arms in this study. One 30-week RCT was not included in the meta-analysis because it did not provide quantitative blood pressure measurements. The study descriptively reported that no changes in

systolic blood pressure were observed between intervention arms, which is inconsistent with the meta-analysis results.[174] (SOE: Moderate; Combination of metformin plus a GLP-1 receptor agonist favored)

Figure 35. Pooled mean between-group difference in systolic blood pressure comparing metformin with a combination of metformin plus a GLP-1 receptor agonist



CI = confidence interval; GLP-1 = glucagon-like peptide-1; ES = effect size (mean between-group difference in the change from baseline); mmHg = millimeters mercury
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

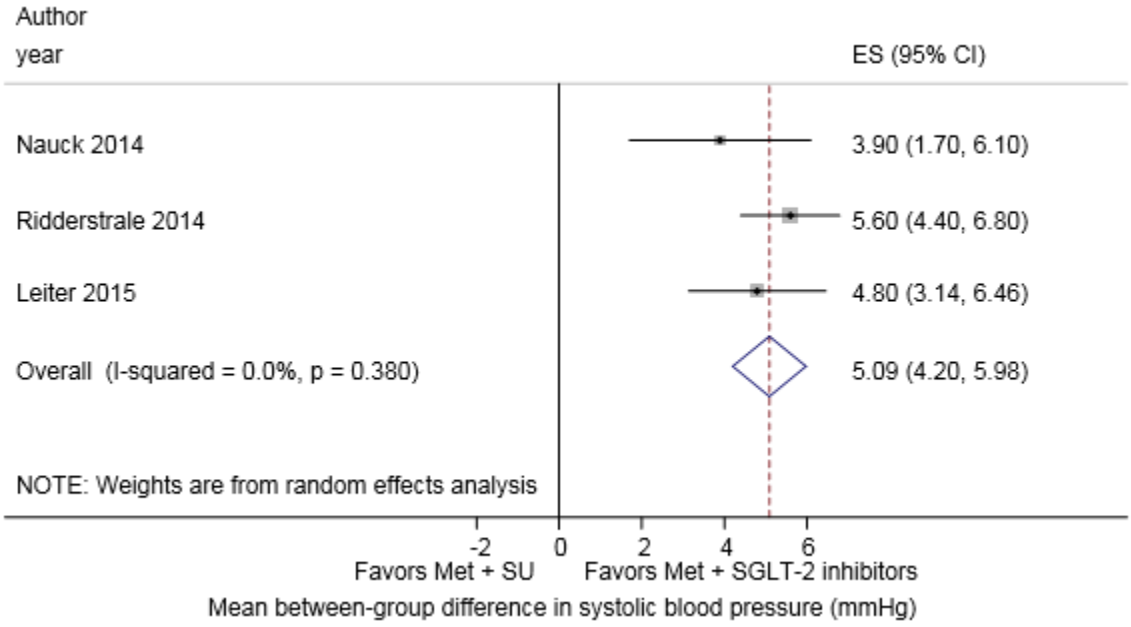
One 26-week RCT compared metformin plus pioglitazone with metformin plus weekly exenatide, reporting a non-significant between-group difference in systolic blood pressure of 2.0 mmHg (95% CI, -0.8 mmHg to 4.8 mmHg).[188] The metformin plus pioglitazone combination decreased mean systolic blood pressure by 1.6 mmHg, and the metformin plus exenatide combination decreased mean systolic blood pressure by 3.6 mmHg. (SOE: Low; Neither combination favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Three 104-week RCTs compared metformin plus a sulfonylurea with metformin plus a SGLT-2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin), favoring SGLT-2 inhibitors in systolic blood pressure reduction.[200, 201, 219] The pooled between-group difference in systolic blood pressure was 5.1 mmHg (95% CI, 4.2 mmHg to 6.0 mmHg) (Figure 36), favoring combinations with a SGLT-2 inhibitor for lowering blood pressure. No single study influenced

the results, and no substantial heterogeneity was found. A 208-week extension study was consistent with the pooled results favoring greater systolic blood pressure reduction with the SGLT-2 inhibitor arm.[54, 219] (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 36. Pooled mean between-group difference in systolic blood pressure comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); Met = metformin; mmHg = millimeters mercury; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Four RCTs comparing metformin plus a sulfonylurea with metformin plus a GLP-1 receptor agonist reported systolic blood pressure, favoring the combination of metformin plus a GLP-1 receptor agonist for lowering blood pressure.[53, 141, 202, 204] These studies were not combined in a meta-analysis due to differences in the duration and absence of sufficient data.[53] One 16-week RCT compared metformin plus glimepiride with metformin plus exenatide and showed a non-significant between-group difference in systolic blood pressure of 2.0 mmHg (95% CI, -12.5 mmHg to 16.5 mmHg) with both combinations decreasing mean systolic blood pressure.[202]

One 16-week RCT compared metformin plus glimepiride with metformin plus liraglutide, showing a significantly greater reduction in systolic blood pressure, by more than 3 mmHg, with the liraglutide combination arms compared with 0.91 mmHg in the glimepiride combination arm ($P < 0.05$).[204] There was a differential loss to followup, with 46 percent to 59 percent, in the higher liraglutide dose arms compared with 16 percent in the metformin plus sulfonylurea arm. One 104-week RCT compared metformin plus glimepiride with metformin plus albiglutide, showing a significant between-group difference in systolic blood pressure favoring the GLP-1

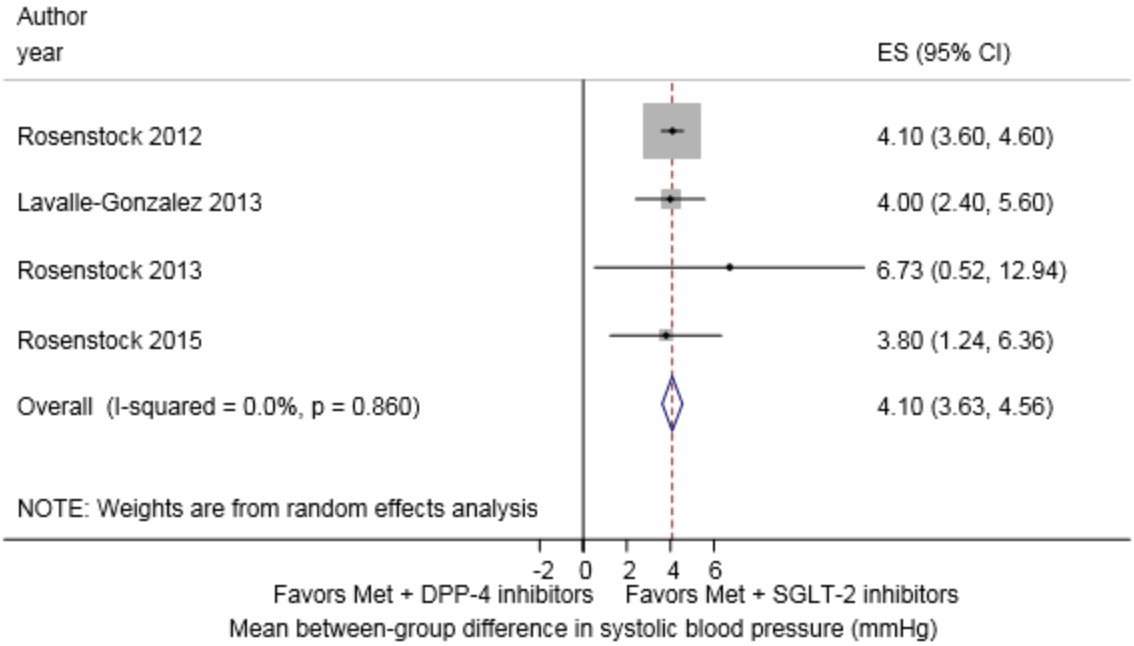
receptor agonist combination by 2.5 mmHg (95% CI, 0.3 mmHg to 4.7 mmHg).[141] The metformin plus glimepiride increased mean systolic blood pressure by 1.5 mmHg while the metformin plus albiglutide arm decreased mean systolic blood pressure by 1.0 mmHg. (SOE: Low; Combination of metformin plus a GLP-1 receptor agonist favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

We pooled four short-duration RCTs comparing metformin plus a DPP-4 inhibitor versus metformin plus a SGLT-2 inhibitor.[153, 156, 158, 209] The pooled results showed a between-group difference in systolic blood pressure of 4.1 mmHg (95% CI, 3.6 mmHg to 4.6 mmHg) (Figure 37), favoring metformin plus SGLT-2 inhibitors. The DPP-4 inhibitor combinations changed mean systolic blood pressure by +0.3 mmHg to -1.8 mmHg, while the SGLT-2 inhibitor combinations consistently decreased mean systolic blood pressure by 3.5 mmHg to 8.5 mmHg. No single study markedly influenced the results, and there was no substantial heterogeneity.

We excluded one 104-week RCT from the meta-analysis due to its long duration.[90] The trial compared metformin plus sitagliptin with metformin plus empagliflozin. The trial showed a between-group difference in systolic blood pressure of 5.1 mmHg (95% CI, 1.0 mmHg to 9.2 mmHg) with metformin plus 10 mg of empagliflozin and 4.8 mmHg (95% CI, 0.7 mmHg to 8.9 mmHg) with metformin plus 25 mg of empagliflozin, favoring the combination arm with a SGLT-2 inhibitor.[90] These results were consistent with the results from the meta-analysis. The metformin plus sitagliptin arm increased mean systolic blood pressure by 1.8 mmHg, and the metformin plus empagliflozin arms decreased mean systolic blood pressure by 3 mmHg to 3.3 mmHg. (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 37. Pooled mean between-group difference in systolic blood pressure comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; ES = effect size (mean between-group difference in the change from baseline); Met = metformin; mmHg = millimeters mercury; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Four RCTs comparing metformin plus a DPP-4 inhibitor with metformin plus a GLP-1 receptor agonist showed no clear differences between-groups.[141, 159, 188, 210] We did not combine these RCTs in a meta-analysis because of differences in drug type and study duration.

One 26-week RCT compared metformin plus sitagliptin with metformin plus exenatide and showed a between-group difference in systolic blood pressure of 4.0 mmHg (95% CI, 1.5 mmHg to 6.5 mmHg), favoring the combination arm with GLP-1 receptor agonists. The metformin plus DPP-4 inhibitor arm increased mean systolic blood pressure by 0.2 mmHg, and the metformin plus GLP-1 receptor agonist arm decreased mean systolic blood pressure by 3.6 mmHg.[188] A 26-week RCT compared metformin plus sitagliptin with metformin plus liraglutide, showing a non-significant between-group difference in systolic blood pressure of 0.4 mmHg (95% CI, -2.0 mmHg to 2.7 mmHg) with metformin plus 1.2 mg of liraglutide and 0.2 mmHg (95% CI, -2.1 mmHg to 2.6 mmHg) with metformin plus 1.8 mg of liraglutide.[210] All arms decreased mean systolic blood pressure.

Among the newest studies, one 52-week RCT compared metformin plus sitagliptin with metformin plus dulaglutide and showed a non-significant between-group difference in systolic blood pressure of 0 mmHg (95% CI, -1.9 mmHg to 1.9 mmHg) with 0.75 mg of dulaglutide weekly and 0.3 mmHg (95% CI, -1.6 mmHg to 2.2 mmHg) with 1.5 mg of dulaglutide weekly.[159] All arms decreased mean systolic blood pressure. One 104-week RCT compared metformin plus sitagliptin with metformin plus albiglutide and showed a non-significant

between-group difference in systolic blood pressure of 1.2 mmHg (95% CI, -1.1 mmHg to 3.5 mmHg).[141] The metformin plus DPP-4 inhibitor arm increased mean systolic blood pressure by 0.2 mmHg, and the metformin plus GLP-1 receptor agonist arm decreased mean systolic blood pressure by 1.0 mmHg. (SOE: Low; Neither combination favored)

Strength of Evidence for Systolic Blood Pressure

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 13, Table 14, and Table 15 and summarized in the Key Points. All studies were RCTs. Study limitations for all the comparisons were low or medium. In general, we did not find strong differences in outcomes in the lower-quality versus higher-quality studies. We were unable to assess publication bias given the limited number of studies for each comparison for systolic blood pressure. We also did not find any evidence of publication bias or reporting bias in the grey literature review. We considered this outcome direct, since systolic blood pressure is strongly linked with important long-term clinical outcomes.[220-222]

Table 13. Strength of evidence domains for monotherapy comparisons in terms of systolic blood pressure among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. SGLT-2 inhibitors	4 (1651)	Medium	Consistent	Direct	Precise	Undetected	Moderate	SGLT-2 inhibitors favored; 2.8 mmHg (2.6 to 3.0 mmHg)
Metformin vs. GLP-1 receptor agonists	2 (820)	Low	Inconsistent	Direct	Precise	Undetected	Low	Neither drug favored
TZD vs. GLP-1 receptor agonists	2 (1048)	Low	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
SU vs. GLP-1 receptor agonists	1 (746)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither drug favored
DPP-4 inhibitors vs. SGLT-2 inhibitors	1 (899)	Low	Unknown	Direct	Imprecise	Undetected	Low	SGLT-2 inhibitors favored
DPP-4 inhibitors vs. GLP-1 receptor agonists	2 (860)	Low	Consistent	Direct	Precise	Undetected	Low	Neither drug favored

DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.

Table 14. Strength of evidence domains for metformin versus metformin-based combination comparisons in terms of systolic blood pressure among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + SGLT-2 inhibitors (shorter studies)	7 (3988)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitors favored; 4.4 mmHg (2.9 to 6.0 mmHg)
Metformin vs. metformin + SGLT-2 inhibitors (longer studies)	2 (728)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + GLP-1 receptor agonists	5 (2688)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin + GLP-1 receptor agonists favored; 3.1 mmHg (1.4 to 4.9 mmHg)

DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.

Table 15. Strength of evidence domains for metformin-based combination comparisons in terms of systolic blood pressure among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + TZD vs. metformin + GLP-1 receptor agonists	1 (514)	Low	Unknown	Direct	Precise	Undetected	Low	Neither combination favored
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration studies)	3 (3815)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitors favored; 5.0 mmHg (4.2 to 6.0 mmHg)
Metformin + SU vs. metformin + GLP-1 receptor agonists	4 (3049)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 receptor agonists favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	5 (3423)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + SGLT-2 inhibitors favored; 4.1 mmHg (3.6 to 4.6 mmHg)
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 receptor agonists	4 (3322)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither combination favored

DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Heart Rate

Monotherapy Comparisons

Metformin Versus SGLT-2 Inhibitors

Two RCTs compared metformin with SGLT-2 inhibitors and showed no differences in heart rate between the arms.[89, 90] One 12-week RCT compared metformin with dapagliflozin, showing a non-significant between-group difference in heart rate of 2.1 beats per minute (bpm) (95% CI, -1.3 bpm to 5.5 bpm) with 5 mg of dapagliflozin and 1.1 bpm (95% CI, -2.4 bpm to 4.7 bpm) with 10 mg of dapagliflozin. The metformin arm increased mean heart rate by 1.1 bpm, and the SGLT-2 inhibitor arms decreased mean heart rate by 0.03 bpm to 1 bpm.[89] The other 90-week RCT compared metformin and empagliflozin and reported that "reductions in blood pressure were not associated with increases in heart rate."[90] (SOE: Low; Neither drug favored)

Metformin Versus GLP-1 Receptor Agonists

Two RCTs compared metformin with a GLP-1 receptor agonist and showed no clear differences in heart rate between the arms.[73, 91] One RCT, with 20 percent loss to followup, compared metformin with two doses of dulaglutide, over 52 weeks. There was a non-significant between-group difference in heart rate of 0.5 bpm (95% CI, -1.1 bpm to 2.1 bpm) with 0.75 mg of dulaglutide weekly and 0.7 bpm (95% CI, -0.9 bpm to 2.3 bpm) with 1.5 mg of dulaglutide weekly. All arms had an increase in mean heart rate.[91] One 26-week RCT compared metformin with exenatide and showed a non-significant between-group difference in heart rate of 1.2 bpm (95% CI, -0.5 bpm to 2.9 bpm). The metformin arm had a mean heart rate increase of 0.3 bpm, and the GLP-1 receptor agonist arm had an increase of 1.5 bpm.[73] (SOE: Moderate; Neither drug favored)

Thiazolidinediones Versus GLP-1 Receptor Agonists

One double-blind, 26-week RCT compared pioglitazone titrated to 45 mg daily with exenatide (2 mg weekly) and showed a between-group difference in heart rate of 3.2 bpm (95% CI, 1.3 bpm to 5.0 bpm).[73] In this study, the pioglitazone arm decreased mean heart rate by 1.7 bpm, and the GLP-1 receptor agonist arm increased mean heart rate by 1.5 bpm. (SOE: Low; Thiazolidinediones favored)

Sulfonylureas Versus GLP-1 Receptor Agonists

One 104-week RCT compared glimepiride with liraglutide, 1.2 mg and 1.8 mg, and showed a non-significant between-group difference in heart rate of 1.4 bpm (95% CI, -0.2 bpm to 2.9 bpm) for the lower dose and 0.2 bpm (95% CI, -1.3 bpm to 1.8 bpm) for the higher dose, favoring glimepiride.[113] The sulfonylurea arm increased the mean heart rate by 0.6 bpm, and the liraglutide arms increased mean heart rate between 0.9 bpm to 2.0 bpm. There was high loss to followup of 50 percent to 60 percent among all arms in this study. (SOE: Low; Neither drug favored)

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

One 24-week RCT compared 100 mg of sitagliptin to empagliflozin, 10 mg and 25 mg, and showed a non-significant between-group difference in heart rate of 0.2 bpm (95% CI, -1.5 bpm

to 1.9 bpm) with 10 mg of empagliflozin and 0.5 bpm (95% CI, -2.2 bpm to 1.2 bpm) with 25 mg of empagliflozin, favoring empagliflozin.[114] The DPP-4 inhibitor arm increased mean heart rate by 0.2 bpm; lower dose empagliflozin increased mean heart rate by 0.02 bpm, and the higher dose decreased mean heart rate by 0.25 bpm. (SOE: Low; Neither drug favored)

DPP-4 Inhibitors Versus GLP-1 Receptor Agonists

One 26-week RCT compared sitagliptin with exenatide and showed a non-significant between-group difference in heart rate of 1.0 bpm (95% CI, -0.9 bpm to 2.9 bpm). Both arms increased mean heart rate.[73] (SOE: Low; Neither drug favored)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Three RCTs comparing metformin to a combination of metformin plus a SGLT-2 inhibitor had inconsistent results.[156, 165, 169] We did not combine the studies in a meta-analysis due to differences in study duration.

One 12-week RCT compared metformin to metformin plus canagliflozin. Compared to metformin, the between-group difference in heart rate was 1.9 bpm lower (95% CI, 1.5 bpm to 2.3 bpm) with metformin plus 100 mg of canagliflozin, 1.1 bpm (95% CI, 0.7 bpm to 1.5 bpm) lower with metformin plus 200 mg of canagliflozin, and 3.4 bpm (95% CI, 3.0 bpm to 3.8 bpm) lower with metformin plus 300 mg of canagliflozin.[156] In this study, the mean heart rate increased by 1.7 bpm in the metformin arm and decreased by 1.7 bpm in the metformin plus 300 mg of canagliflozin arm.

One 18-week RCT compared metformin with metformin plus canagliflozin and reported a between-group difference in heart rate of 0.9 bpm with 100 mg of canagliflozin daily and 1.4 bpm with 300mg of canagliflozin daily. Metformin caused no increase in mean heart rate, and metformin plus canagliflozin increased mean heart rate.[165]

A 102-week RCT, with over 20 percent loss to followup, compared metformin to metformin plus 10 mg of dapagliflozin and showed a non-significant between-group difference in heart rate of 0.1 bpm (95% CI, -2.8 bpm to 3.0 bpm). Both arms increased mean heart rate slightly.[169] (SOE: Low; Neither drug favored)

Metformin Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

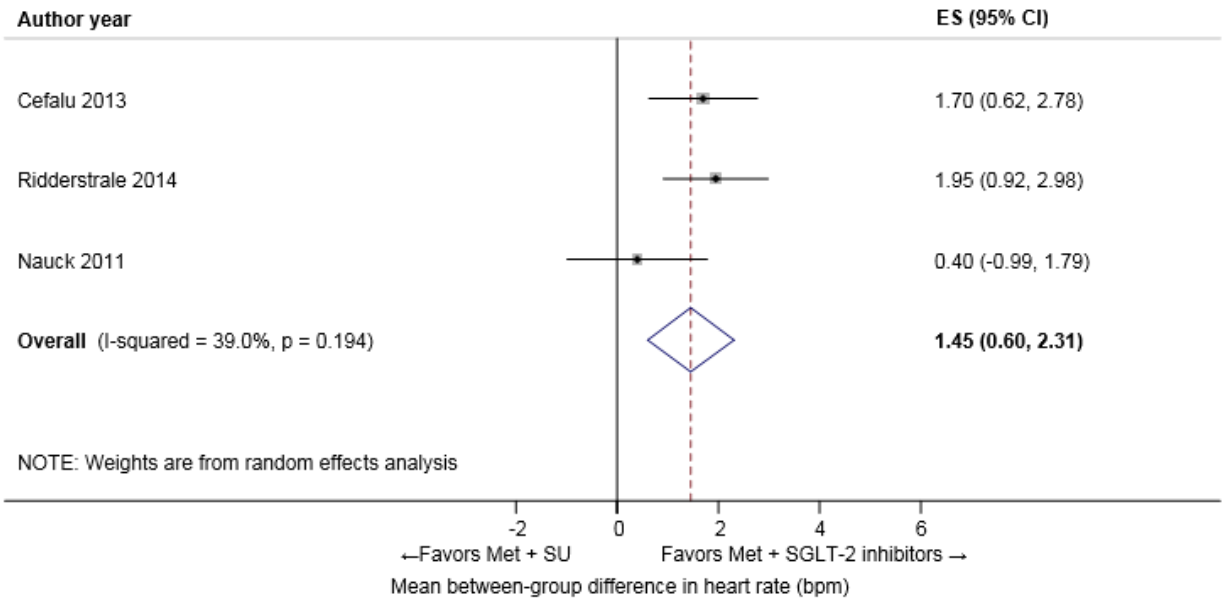
Three RCTs compared metformin to a combination of metformin plus a GLP-1 receptor agonist, with conflicting results.[141, 159, 174] The 104-week RCT compared metformin to metformin plus albiglutide and showed a non-significant between-group difference in heart rate of 1.0 bpm (95% CI, -1.2 bpm to 3.2 bpm), favoring metformin.[141] A 26-week RCT compared metformin to metformin plus dulaglutide and showed a between-group difference in heart rate of 2.8 bpm (95% CI, 1.1 bpm to 4.5 bpm), favoring metformin. There was high loss to followup of at least 60 percent in all arms in this study.[159] One 30-week RCT compared metformin with metformin plus exenatide. The study reported that no changes in heart rate were observed between intervention arms (no quantitative data available).[174] (SOE: Insufficient)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

We pooled three RCTs, each more than 1 year in duration, that compared metformin plus a sulfonylurea with metformin plus a SGLT-2 inhibitor (Figure 38).[198-200] A 104-week extension study compared metformin and glimepiride with metformin and canagliflozin, showing a between-group difference of 0.9 bpm (insufficient data to calculate 95% CI). The glimepiride arm increased heart rate by 0.7 bpm, and the canagliflozin arm decreased heart rate by 0.2 bpm, which is consistent with the pooled results.[198, 201] (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored)

Figure 38. Pooled mean between-group difference in heart rate comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor



bpm = beats per minute; CI = confidence interval; ES = effect size (mean between-group difference in the change from baseline); Met = metformin; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Two RCTs compared metformin plus a sulfonylurea with metformin plus a GLP-1 receptor agonist, with conflicting results.[53, 141] One RCT, with 75 percent losses to followup, reported that mean heart rate increased by 1.2 bpm ($P = 0.024$) with metformin plus exenatide but not with metformin plus glimepiride (0.6 bpm; $P = 0.28$), with no differences between groups at any time.[53] One 104-week RCT, with 30 percent loss to followup, compared metformin plus glimepiride with metformin plus albiglutide and showed a between-group difference of 1.8 bpm (95% CI, 0.2 bpm to 3.4 bpm), favoring the metformin with glimepiride treatment.[141] The

sulfonylurea combination decreased mean heart rate by 0.5 bpm, and the GLP-1 receptor agonist combination increased mean heart rate by 1.3 bpm. (SOE: Insufficient)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Two RCTs compared metformin plus a DPP-4 inhibitor to metformin plus a SGLT-2 inhibitor and showed no clear differences between groups in heart rate.[90, 156] One 12-week RCT compared metformin plus sitagliptin with three dose strengths of metformin plus canagliflozin. The RCT showed a non-significant between-group difference in heart rate of 1.5 bpm (95% CI, 1.2 bpm to 1.8 bpm) with 100 mg of canagliflozin, 2.3 bpm (95% CI, 2.0 bpm to 2.6 bpm) with 200 mg of canagliflozin, and 0.0 bpm (95% CI, -0.4 bpm to 0.4 bpm) with 300 mg of canagliflozin.[156] The DPP-4 inhibitor with metformin decreased mean heart rate by 1.7 bpm; 100 mg of canagliflozin with metformin decreased mean heart rate by 0.2 bpm, 200 mg increased mean heart rate by 0.6 bpm, and 300 mg decreased mean heart rate by 1.7 bpm. One 90-week RCT compared metformin plus sitagliptin to metformin plus empagliflozin and found no increase in heart rate accompanying blood pressure reduction.[90] (SOE: Low; Neither combination favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Three RCTs compared metformin plus a DPP-4 inhibitor with metformin plus a GLP-1 receptor agonist.[141, 159, 210] These studies were not combined in a meta-analysis due to differences in study duration.

The two short studies significantly favored the combination of metformin plus a DPP-4 inhibitor. One 26-week RCT compared metformin plus sitagliptin with metformin plus liraglutide and showed a between-group difference in heart rate of 3.0 bpm (95% CI, 1.4 bpm to 4.5 bpm) with 1.2 mg of liraglutide and 4.6 bpm (95% CI, 3.0 bpm to 6.1 bpm) with 1.8 mg of liraglutide. The DPP-4 inhibitor combination decreased mean heart rate by 0.64 bpm, and the GLP-1 combinations increased mean heart rate by 2.3 bpm and 3.9 bpm.[210] A 52-week RCT, with over 60 percent loss to followup, compared metformin plus sitagliptin to metformin plus dulaglutide, showing a between-group difference in heart rate of 2.4 bpm (95% CI, 1.0 bpm to 3.8 bpm) with 0.75 mg of dulaglutide weekly and 2.7 bpm (95% CI, 1.3 bpm to 4.1 bpm) with 1.5 mg of dulaglutide weekly. The DPP-4 inhibitor combination decreased mean heart rate by 0.3 bpm, and the GLP-1 combinations increased mean heart rate by 2.1 and 2.4 bpm.[159]

The 104-week RCT, with over 30% loss to followup, compared metformin plus sitagliptin to metformin plus albiglutide and showed a non-significant between-group difference in heart rate of 0.5 bpm (95% CI, -1.2 bpm to 2.2 bpm). Both arms increased mean heart rate slightly.[141] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored)

Strength of Evidence for Heart Rate

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 16, Table 17, and Table 18 and summarized in the Key Points. All studies were RCTs. Study limitations for all comparisons were low or medium. Where quality influenced the study results, we describe that under the appropriate comparisons. In general, we did not find strong differences in outcomes in the lower-quality versus higher-quality studies. We were unable to assess publication bias given the limited number of studies for

each comparison for heart rate. We also did not find any evidence of publication bias or reporting bias in the grey literature review. We considered this outcome indirect, since there is limited evidence directly linking heart rate to mortality or other clinical outcomes, including among adults with diabetes.

Table 16. Strength of evidence domains for monotherapy comparisons in terms of heart rate among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. SGLT-2 inhibitors	2 (1048)	Medium	Consistent	Indirect	Imprecise	Undetected	Low	Neither drug favored
Metformin vs. GLP-1 receptor agonists	2 (820)	Low	Consistent	Indirect	Precise	Undetected	Moderate	Neither drug favored
TZD vs. GLP-1 receptor agonists	1 (820)	Low	Unknown	Indirect	Precise	Undetected	Low	TZD favored
SU vs. GLP-1 receptor agonists	1 (746)	Medium	Unknown	Indirect	Precise	Undetected	Low	Neither drug favored
DPP-4 inhibitors vs. SGLT-2 inhibitors	1 (899)	Low	Unknown	Indirect	Precise	Undetected	Low	Neither drug favored
DPP-4 inhibitors vs. GLP-1 receptor agonists	1 (820)	Low	Unknown	Indirect	Precise	Undetected	Low	Neither drug favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.

Table 17. Strength of evidence domains for metformin versus metformin-based combination comparisons in terms of heart rate among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + SGLT-2 inhibitors	3 (912)	Low	Inconsistent	Indirect	Imprecise	Undetected	Low	Neither drug favored
Metformin vs. metformin + GLP-1 receptor agonists	3 (2473)	Low	Inconsistent	Indirect	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.

Table 18. Strength of evidence domains for metformin-based combination comparisons in terms of heart rate among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + SU vs. metformin +SGLT-2 inhibitors (longer duration studies)	3 (3815)	Low	Consistent	Indirect	Precise	Undetected	Moderate	Metformin + SGLT-2 inhibitor favored; mean between-group difference, 1.5 bpm (95% CI, 0.6 to 2.3 bpm)
Metformin + SU vs. metformin +GLP-1 receptor agonists	2 (2078)	Medium	Inconsistent	Indirect	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	2 (1110)	Medium	Consistent	Indirect	Imprecise	Undetected	Low	Neither combination favored
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 receptor agonists	3 (2808)	Medium	Inconsistent	Indirect	Precise	Undetected	Low	Metformin + DPP-4 inhibitor favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled mean between-group differences (95 percent confidence intervals). We only include estimates for comparisons with high or moderate strength of evidence.

Key Questions 2a and 2b: All-Cause Mortality and Macrovascular and Microvascular Outcomes

Study Design and Population Characteristics

One hundred and eighteen studies (in 141 publications) reported on the comparative effectiveness of oral diabetes medications on long-term outcomes of interest (Appendix D, Tables D5 to D9). Twenty studies occurred in North America, 19 studies occurred in Europe, 13 studies occurred in Asia; all others were multi-continent studies.

Ninety-six studies were RCTs, with durations from 12 weeks to 5.5 years. Thirty-four of the RCTs lasted for at least one year. All studies specified intermediate, not long-term, outcomes as their primary outcome (see Key Question 1) but then also reported the incidence of one or more long-term outcomes (e.g., mortality), usually as an adverse event. Two studies used a cross-over design.[223, 224] Eighty-two RCTs reported support from a pharmaceutical company. Eighteen of the 62 (29%) RCTs identified in this update did not report on rescue therapy; rescue therapy was allowed in 25 studies (40%) and was not allowed in 15 studies (24%).

We also included 21 retrospective cohort studies and one case-control study; duration of followup ranged from 6 months to over 5 years (eight lasted less than 2 years, 12 lasted 2 years or longer, and one lasted at least 12 months but did not specify the mean followup). These studies analyzed data from 12 unique cohorts, including five studies from Danish national databases[225-229] and one from the Saskatchewan Health Database.[230] Seven of the observational studies were designed to explicitly evaluate cardiovascular outcomes.[151, 225-229, 231] Six observational studies reported support from a pharmaceutical company.

The mean age of participants ranged from 48 years to 75 years, with the majority of studies reporting a mean age in the upper 50s. About 50 percent of participants were female. Forty-seven studies did not report race or ethnicity. In the studies that reported race, the majority of the participants were Caucasians. Two RCTs reported greater than 25 percent African American participants,[118, 232] and two studies reported 70 to 80 percent Hispanic participants.[121, 186] Most trials excluded people with coexisting illness, such as renal, cardiovascular, or liver disease.

Risk of Bias

Ninety-six RCTs were included in this section, all of which were described as randomized. Fifty-eight percent of the trials described their randomization scheme and another 74 percent of the trials were described as being double-blinded. Forty-five percent of all double-blinded RCTs also described the steps taken to ensure blinding. The majority of the trials (87 percent) described the withdrawals and dropouts. Of the 11 RCTs with at least 2 years of followup, ten had over 20 percent losses to followup.

Of the 21 observational studies included in this section, 100 percent reported characteristics of subjects and tests of interest, 95 percent reported actual P values, and 85 percent described the measurement of outcomes of interest. All studies described and adjusted for confounding factors and conducted statistical analyses. All of the observational studies described the number of participants who were lost to followup after the start of the period of observation.

Key Points and Evidence Grades

All-Cause Mortality

- All evidence on all-cause mortality was of low strength or insufficient.

Cardiovascular Mortality

- Sulfonylurea monotherapy was associated with increased cardiovascular mortality compared with metformin monotherapy (relative risk range 1.5 to 1.7 from individual RCTs; range in risk differences, 0.1 to 2.9%; range in duration of follow up, 2.8 to 4.0 years). (SOE: Moderate)
- To date, there has been uncertainty about the cardiovascular benefits of diabetes medications as evidenced by the FDA labeling stating a lack of known lower macrovascular risk for any diabetes medications; still, all evidence on the comparative effectiveness of the included diabetes medications on cardiovascular mortality was of low strength or insufficient.

Cardiovascular and Cerebrovascular Disease Morbidity

- To date, there has been uncertainty about the cardiovascular benefits of diabetes medications as evidenced by the FDA labeling stating a lack of known lower macrovascular risk for any diabetes medications; still, all evidence on the comparative effectiveness of the included diabetes medications on cardiovascular morbidity was of low strength or insufficient.

Retinopathy, Nephropathy, and Neuropathy

- The evidence was low or insufficient for all comparisons, and almost all RCTs were short-term.

Evidence for All-Cause Mortality

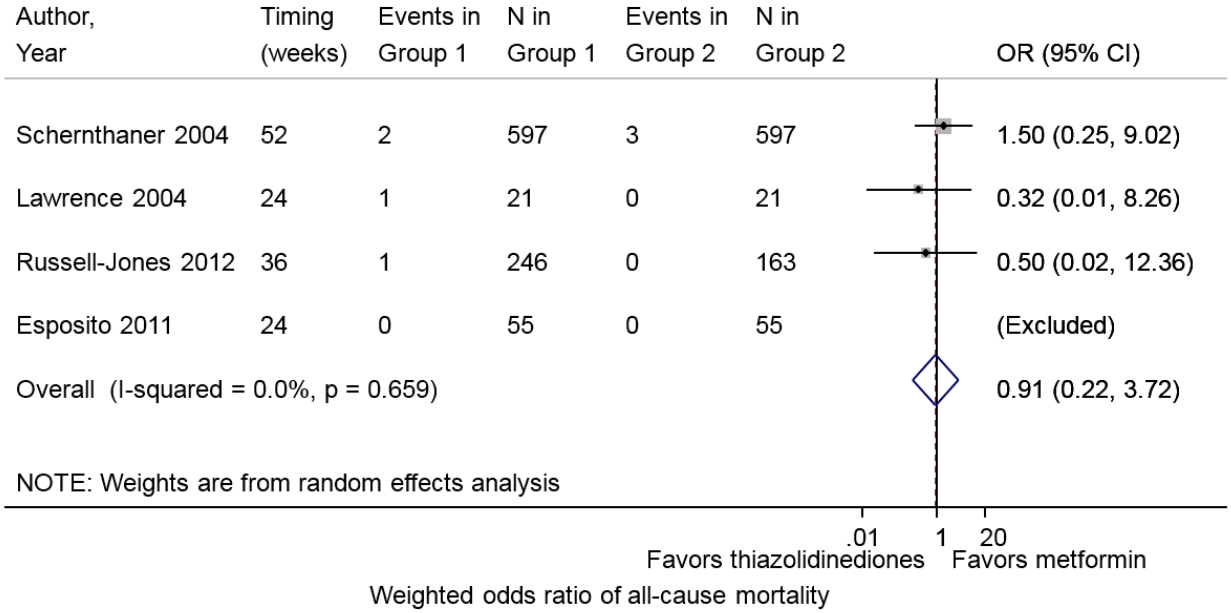
Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Randomized Controlled Trials

Four RCTs, each lasting 24 to 52 weeks, compared the effects of metformin with pioglitazone and found similar risks of all-cause mortality in the metformin and pioglitazone arms with seven deaths across the studies (pooled OR for metformin versus pioglitazone, 0.91; 95% CI, 0.22 to 3.72) (Figure 39).[62, 63, 73, 76] We found no evidence of statistical heterogeneity. Omission of any single study did not change the conclusions. Deaths were not described in the pioglitazone arm of one study, so we imputed "0" events in this arm for the meta-analysis.[76] The pooled between-group difference in mortality for metformin versus placebo was 0.0% (95% CI, -0.6 to 0.6%).

Figure 39. Pooled odds ratio of short-term all-cause mortality comparing metformin with pioglitazone



CI = confidence interval; Group 1 = metformin; Group 2 = thiazolidinediones; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Two RCTs compared the effects of metformin with rosiglitazone on all-cause mortality.[50, 59] The A Diabetes Outcome Progression Trial (ADOPT) randomized participants with recently-diagnosed, untreated type 2 diabetes from 488 different centers in the United States, Canada, and Europe to rosiglitazone, metformin, or glyburide and had long-term follow up.[50] Mortality was slightly lower in the metformin (31/1454; 2.1%) versus rosiglitazone (34/1456; 2.3%) arm with median followup of 4.0 years.[50] The actual number of participants for which ADOPT ascertained mortality is unclear, and withdrawals were high across the arms: 37 percent (rosiglitazone) and 38 percent (metformin).[50] The second trial was 32 weeks in duration and reported no deaths in the metformin or rosiglitazone arms.[59]

Observational Studies

Two retrospective cohort studies compared the effects of initiating thiazolidinediones and metformin (Table 19).[233, 234] One study found no significant difference in all-cause mortality for metformin and thiazolidinediones.[233] The second study found a significantly increased risk of all-cause mortality among women but not among men for rosiglitazone versus metformin.[234]

[SOE: Low for pioglitazone (short-term mortality); Neither metformin nor pioglitazone favored] (SOE: Low for rosiglitazone; Metformin favored compared with rosiglitazone)

Table 19. Observational studies comparing metformin with thiazolidinediones on all-cause mortality

Author, Year	Population	Mean Followup	Results
Pantalone, 2009[233]	Cleveland Clinic electronic health record system N not reported	Not reported	HR for rosiglitazone, 1.33, 95% CI, 0.93 to 1.91 HR for pioglitazone, 1.08, 95% CI, 0.78 to 1.51 Reference = metformin
Wheeler, 2013[234]	Veterans Health Administration 2004-2009 n=132,306 (metformin) n=3753 (rosiglitazone)	1.7 years (metformin) 1.4 years (rosiglitazone)	HR for 185,360 men, 1.19; 95% CI, 0.95 to 1.49 HR for 7,812 women, 4.36; 95% CI, 1.34 to 14.20 Reference = metformin *P* interaction for gender = 0.034

CI = confidence interval; HR = hazard ratio

Metformin Versus Sulfonylureas

Randomized Controlled Trials

Six RCTs compared the effects of metformin and a sulfonylurea on all-cause mortality (Table 20).[50, 129, 130, 137, 138, 231]

Two of these RCTs had long-term followup and were of medium quality: The smaller of these two RCTs was conducted in China and had 2.8 years of followup. All participants were required to have documented coronary heart disease. The authors reported more than double the risk of death for the glipizide (mean dose 28.3 mg) arm versus metformin (mean dose 1,400 mg) arm.[231] Losses to followup were 21 percent in both arms of this study.[231] In the other long-term RCT, ADOPT (described above), the absolute difference in mortality was 0.1 percent higher for the sulfonylurea (maximum dose 15 mg; mean dose not reported) arm versus the metformin (maximum dose 2,000 mg; mean dose not reported) arm. As noted, there were high withdrawal rates in this study: 38 percent (metformin) and 44 percent (glyburide). Median followup was less for the sulfonylurea (3.3 years) versus metformin (4.0 years) arm.[50]

The other four RCTs, judged to be at low risk of bias, lasted less than 30 weeks.[129, 130, 137, 138] Three of these studies reported no deaths in either arm;[129, 130, 138] the fourth study reported one death in the metformin arm and none in the sulfonylurea arm.[137]

Table 20. Randomized controlled trials comparing metformin with sulfonylureas on all-cause mortality

Author, Year	Mean Followup	Number of Deaths (%): Metformin Versus Sulfonylurea	Estimate of the Measure of Association (95% CI) (Metformin as Reference Group)
Hong, 2013[231]	2.8 years	7/156 (4.5) versus 14/148 (9.5)	RR, 2.1* (0.9 to 5.1) OR, 2.2* (0.8 to 6.7) RD, 5%* (-0.8% to 10.7%)
Kahn, 2006[50]	4.1 years (median)	31/1454 (2.1) versus 31/1441 (2.2)	RR, 1.0* (0.6 to 1.7) OR, 1.0* (0.6 to 1.7) RD, 0.02%* (-1.0% to 1.1%)
Chien, 2007[138]	16 weeks	0/17 (0.0) versus 0/17 (0.0)	NR
Garber, 2003[129]	16 weeks	0/164 (0.0) versus 0/151 (0.0)	NR
Goldstein, 2003[130]	18 weeks	0/76 (0.0) versus 0/84 (0.0)	NR
DeFronzo, 1995[137]	29 weeks	1/210 (0.5) versus 0/209 (0.0)	NR

CI = confidence interval; NR= not reported; OR = odds ratio; RD = absolute risk difference; RR = relative risk
* Calculated for this report from values published in the study.

Observational Studies

We identified eight relevant retrospective cohort studies based on four cohorts (Veterans Health Administration, n=3;[234-236] Cleveland Clinic electronic health record, n=2;[233, 237] Danish National Patient Health Registry, n=2;[225, 229] and the Health Service Database of Lombardy, n=1[238]). All studies reported an increased risk of death for a sulfonylurea versus metformin (Table 21).

(SOE: Low; Metformin favored for long-term mortality; Neither favored for short-term mortality)

Table 21. Observational studies comparing metformin with sulfonylureas on all-cause mortality

Author, Year	Population	Followup	Number of Deaths (%): Metformin Versus Sulfonylurea	Adjusted Results
Kahler, 2007[235]	Veterans' Health Administration Diabetes Epidemiology Cohort	3 years	82 / 2988 (2.7%) versus 1005 / 19,053 (5.3%)	OR, 0.87; 95% CI, 0.68 to 1.10 Reference = sulfonylurea
Wheeler, 2013[234]	Veterans' Health Administration	222,258 p-years (metformin) 47,604 p-years (glipizide) 48,238 p-years (glibenclamide)	2107 / 132,306 versus 1121 / 28,957 (glipizide) and 912 / 28,156 (glibenclamide)	HR for glipizide, 1.55; 95% CI, 1.43 to 1.67 HR for glibenclamide, 1.38; 95% CI, 1.27 to 1.5 Reference = metformin
Wang, 2014[236]	Veterans' Health Administration – Respondents to Veterans Large Health Survey 1999	5.3 years	NR	HR 0.69; 95% CI, 0.6 to 0.79 Reference = sulfonylurea
Pantalone, 2009[233]	Cleveland Clinic EHR	8 years	NR	HR, 0.54; 95% CI, 0.46 to 0.64 Reference = sulfonylurea
Pantalone, 2012[237]*	Cleveland Clinic EHR	2.2 years (median)	NR / 12,774 (metformin) NR / 4,325 (glipizide) NR / 4,279 (glyburide) NR / 2,537 (glibenclamide)	HR for glipizide, 1.64; 95% CI, 1.39 to 1.94 HR for glyburide, 1.59; 95% CI, 1.35 to 1.88 HR for glibenclamide, 1.68; 95% CI, 1.37 to 2.06 Reference = metformin
Schramm, 2011[229]	National Patient Registry (Denmark) Previous MI	3.3 years (median)	213 / 2906 versus 141 / 660 (glipizide) 737 / 3894 (glimepiride) 265 / 1168 (glibenclamide)	HR for glipizide, 1.53; 95% CI, 1.23 to 1.89 HR for glimepiride, 1.3; 95% CI, 1.11 to 1.51 HR for glibenclamide, 1.47; 95% CI, 1.22 to 1.76 Reference = metformin
	National Patient Registry (Denmark) No previous MI	91.5 weeks	1548 / 43,340 versus 947 / 6965 (glipizide) 4081 / 36,313 (glimepiride) 1546 / 12,495 (glibenclamide)	HR for glipizide, 1.27; 95% CI,1.17 to 1.38 HR for glimepiride, 1.32; 95% CI, 1.24 to 1.4 HR for glibenclamide, 1.19; 95% CI, 1.11 to 1.28 Reference = metformin
Andersson, 2010[225]	National Patient Registry (Denmark) – patients with admission for heart failure (1997-2006)	844 days	239 / 688 (35%) versus 2344 / 3615 (65%)	HR, 0.85; 95% CI, 0.75 to 0.98; *P* = 0.02) Reference = sulfonylurea
Corrao, 2011[238]	Health Services Database of Lombardy	Mean followup 4.8 to 5.1 years	NR / 21,810 versus NR / 48,627	HR, 1.37; 95% CI, 1.26 to 1.49 Reference = metformin

CI = confidence interval; EHR = electronic health record; HR = hazard ratio; MI = myocardial infarction; NR = not reported; OR = odds ratio

* This study population may overlap with Pantalone, 2009.[233]

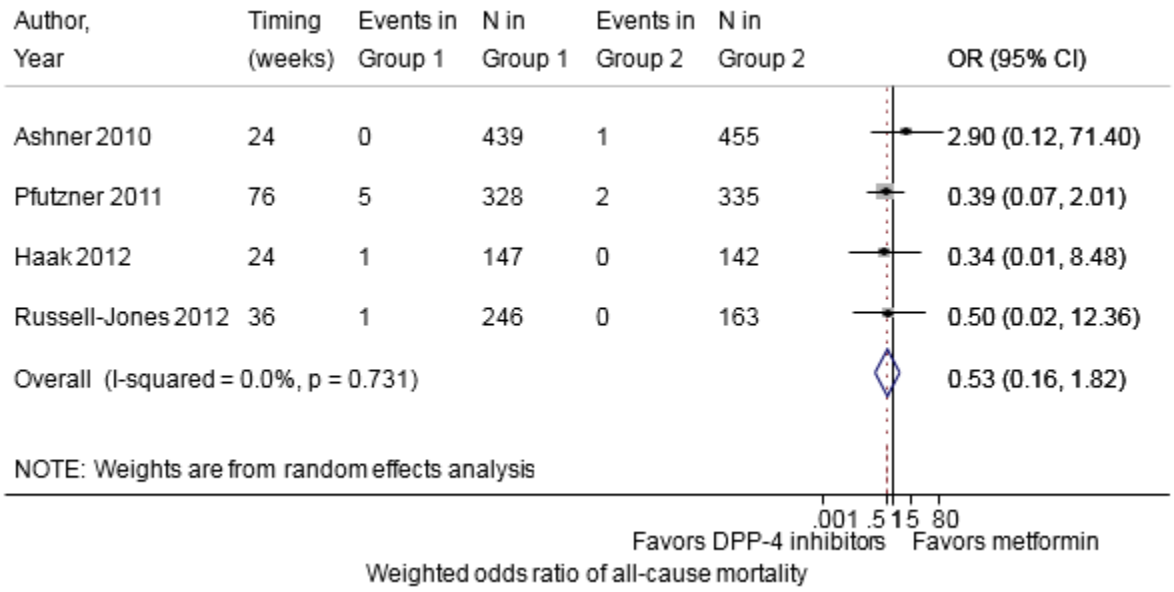
Metformin Versus DPP-4 Inhibitors

Five RCTs compared the effects of metformin with sitagliptin on all-cause mortality. Meta-analysis of the four RCTs with the most similar durations (24 to 76 weeks) showed no difference in all-cause mortality for DPP-4 inhibitors compared with metformin, based on 10 deaths across

the studies (pooled OR, 0.53; 95% CI, 0.16 to 1.82) (Figure 40).[73, 82, 86, 87] We did not find evidence of statistical heterogeneity. One of these RCTs did not report on deaths in the DPP-4 inhibitor arm, and we imputed "0" for this arm.[73] The pooled risk difference for DPP-4 inhibitors versus metformin was -0.1% (95% CI, -0.6 to 0.4%). The fifth RCT compared three metformin arms with sitagliptin 100 mg over 104 weeks. Two deaths were reported in the patients that started on placebo and were switched to metformin at 24 weeks; one death was reported in the metformin arm using 1000 mg as its maximum dose; and no deaths were reported in the metformin arm using 2000 mg as its maximum dose; no deaths occurred in the sitagliptin arm.[85]

A single retrospective cohort study from the Danish National Patient Registry reported on mortality for metformin (3,024/83,528) and sitagliptin (49/1,228) with mean followup of 0.9 to 1.8 years. The adjusted risk ratio (RR) for metformin versus sitagliptin was 1.25 (95% CI, 0.92 to 1.71; $P = 0.15$).[228] (SOE for short-term mortality: Low; Neither treatment favored)

Figure 40. Pooled odds ratio of short-term all-cause mortality comparing metformin with DPP-4 inhibitors



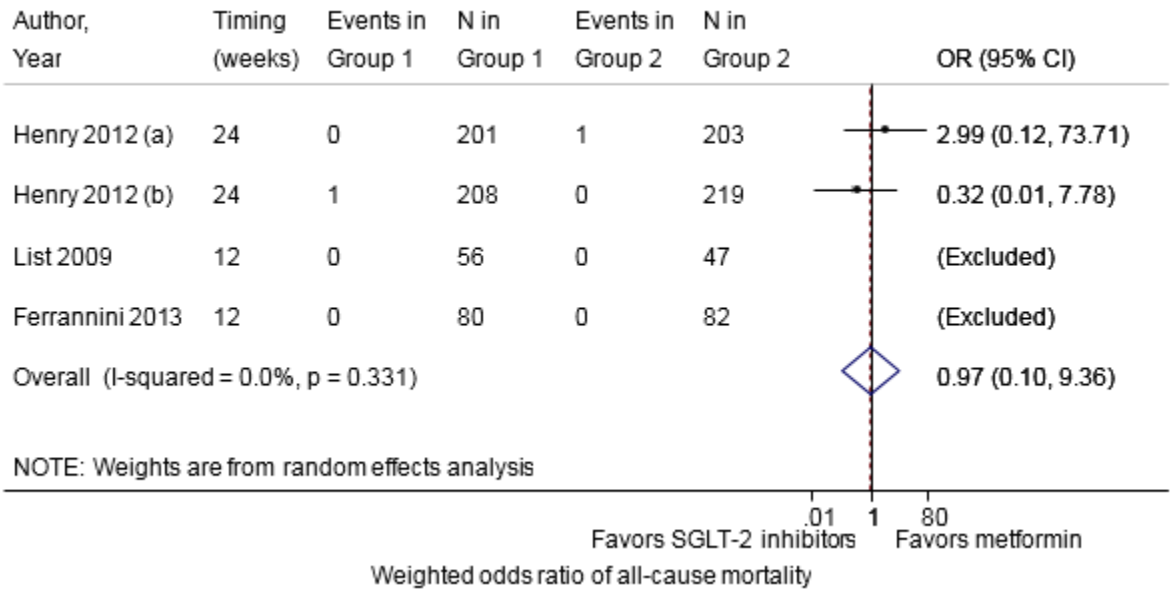
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = dipeptidyl peptidase-4 inhibitors; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus SGLT-2 Inhibitors

Four short-term RCTs (12 to 24 weeks in duration, reported in 3 articles) compared the effects of metformin to SGLT-2 inhibitors on all-cause mortality and found no difference for SGLT-2 inhibitors versus metformin (pooled OR, 0.97; 95% CI, 0.10 to 9.36) (Figure 41).[88, 89, 239] Only two deaths were reported in the studies (one in a metformin arm[88] and one in a SGLT-2 arm[88]). We did not observe significant statistical heterogeneity. Removal of any one study did not change the inference. The pooled risk difference for SGLT-2 inhibitors versus metformin was -0.0% (95% CI, -0.9 to 0.8%) (SOE: Low; Neither favored)

Figure 41. Pooled odds ratio for short-term all-cause mortality comparing metformin with SGLT-2 inhibitors



CI = confidence interval; Group 1 = metformin; Group 2 = sodium-glucose co-transporter-2 inhibitors; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

Metformin Versus GLP-1 Receptor Agonists

Two RCTs compared all-cause mortality between metformin and GLP-1 receptor agonists.[73, 91] In one, lasting 52 weeks, there were no deaths in the metformin or dulaglutide arms.[91] In the other, lasting 36 weeks, one death was reported in the metformin arm (1/246, 0.4%), and deaths were not described in the exenatide once weekly arm.[73] (SOE for short-term mortality: Low; Neither favored)

Thiazolidinediones Versus Sulfonylureas

Randomized Controlled Trials

Three RCTs compared thiazolidinediones with sulfonylureas and reported on mortality. The ADOPT trial reported slightly more deaths in the rosiglitazone arm than in the glyburide arm (2.3% versus 2.2%, respectively; risk difference of 0.1% for rosiglitazone compared with metformin) with differential followup time (median 3.3 years for sulfonylurea and 4.0 years for rosiglitazone) and withdrawals (44% for sulfonylurea and 37% for rosiglitazone).[50] Two short-term trials reported few deaths in either the thiazolidinedione or sulfonylurea arms: One RCT (N=598) reported no deaths in either the rosiglitazone (4 mg and 8 mg) or sulfonylurea arms at 52 weeks.[94] A 56-week trial reported two deaths in the glyburide arm (2/251; 0.8%) and no deaths in the pioglitazone arm (0/251, 0%).[95]

Observational Studies

Two retrospective cohort studies compared the effects of thiazolidinediones with sulfonylureas on all-cause mortality.[233, 234] In the cohort from the Cleveland Clinic (N=20,450), individuals initiating pioglitazone had a statistically significant lower risk of death compared with those initiating a sulfonylurea (adjusted HR, 0.59; 95% CI, 0.43 to 0.81). Those initiating rosiglitazone did not have a statistically significant lower risk of death compared with those initiating a sulfonylurea (adjusted HR, 0.73; 95% CI, 0.51 to 1.02). Followup time was not specified.[233] In the Veterans Health Administration cohort, glipizide and glibenclamide were each compared separately with rosiglitazone.[234] Compared with rosiglitazone, the adjusted RR of death for glipizide users was 1.26 (95% CI, 1.00 to 1.58), and the adjusted RR for glibenclamide users was 1.09 (95% CI, 0.87 to 1.38).[234]

(SOE: Insufficient for comparison of sulfonylurea and pioglitazone) (SOE: Insufficient for comparison of sulfonylurea and rosiglitazone)

Thiazolidinediones Versus DPP-4 Inhibitors

Two RCTs compared pioglitazone with sitagliptin and reported on mortality.[48, 73] The 12-week RCT (N=106) reported no deaths in either arm.[48] The 36-week RCT (N=326) did not report on deaths in the pioglitazone or sitagliptin arms, although it did report on deaths in other study arms.[73] Of note, Russell-Jones 2012, et al. did not use an intention-to-treat approach and had greater than 13 to 18 percent losses to followup across arms.[73] (SOE: Low; Neither favored for short-term mortality)

Thiazolidinediones Versus GLP-1 Receptor Agonists

A single RCT, with 36 weeks of followup, did not report on deaths in the pioglitazone (n=163) or exenatide once weekly (n=248) arms although it did report on deaths in other study arms.[73] (Not graded)

Sulfonylureas Versus DPP-4 Inhibitors

A single RCT reported seven and three deaths over 58 weeks in the glipizide (7/212, 3.3%) and sitagliptin (3/210, 1.4%) arms, respectively.[107] The authors did not use an intention-to-treat approach for mortality, and losses to followup were greater than 19 percent for both arms.[107] (SOE: Low; DPP-4 inhibitors favored for short-term mortality)

Sulfonylureas Versus GLP-1 Receptor Agonists

Two RCTs compared sulfonylureas with liraglutide and reported on all-cause mortality.[110, 113] Liraglutide doses varied across the trials, and death rates were low in both trials (Table 22).[110, 113] In the longer study (104 weeks), mortality was higher in the sulfonylurea arm compared with the low-dose liraglutide arm (0.4% vs. 0.0%) but similar to that in the high-dose liraglutide arm (0.4%).[113] (SOE: Insufficient)

Table 22. Randomized controlled trials comparing sulfonylureas with GLP-1 receptor agonists on all-cause mortality

Author, Year	Followup (Weeks)	Sulfonylurea (Dose*)	Liraglutide (Dose*)	Number of Deaths / N (%) in the Sulfonylurea Arm	Number of Deaths / N (%) in the Liraglutide Arm
Kaku, 2011[110]	52	Glibenclamide (fixed at 1.25 to 2.5 mg)	Liraglutide (max 0.9 mg)	NR/132	1/268 (0.4)
Garber, 2011[113]	104	Glimepiride (max 8 mg)	Liraglutide (max 1.2 mg)	1/248 (0.4)	0/251 (0)
		Glimepiride (max 8 mg)	Liraglutide (max 1.8 mg)	1/248 (0.4)	1/247 (0.4)

GLP-1 = glucagon-like peptide-1; max = maximum; mg = milligrams
* All doses were titrated, unless otherwise stated.

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

Two RCTs compared sitagliptin with a SGLT-2 inhibitor (followup 24 to 26 weeks).[114, 240] No deaths occurred in one study (N=670),[114] and one death was reported in the sitagliptin arm (1/155, <1%) of the other study (no deaths in the SGLT-2 inhibitor arms; N=495).[240] Neither study used an intention-to-treat approach for mortality, and losses to followup ranged from 3 to 13 percent across the arms of the trials.[114, 240] (SOE: Insufficient)

DPP-4 Inhibitors Versus GLP-1 Receptor Agonists

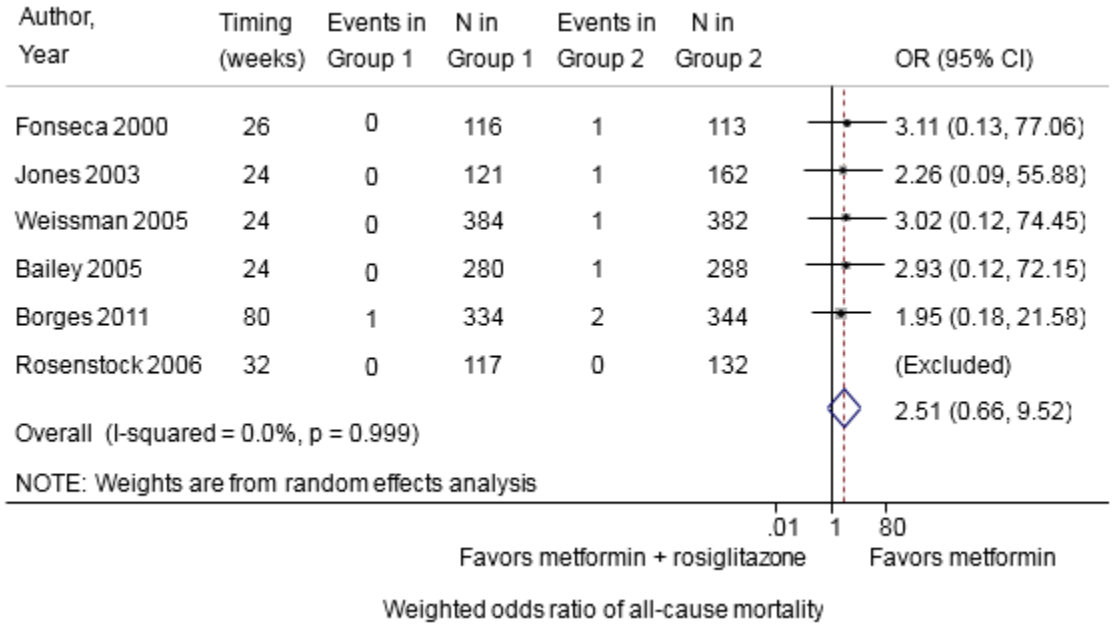
A single RCT compared sitagliptin (n=163) with exenatide (n=248) and did not report on deaths in either arm, although it did report on deaths in other study arms.[73] (SOE: Insufficient)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Six articles reported the results from seven RCTs (durations ranging from 24 to 80 weeks) on the effects of metformin versus metformin plus rosiglitazone on all-cause mortality.[59, 119, 120, 123, 127, 241] The combined OR comparing metformin plus rosiglitazone with metformin was 2.51 (95% CI, 0.66 to 9.52; $I^2 = 0.0\%$) (Figure 42), showing a non-significant increased risk of death with metformin plus rosiglitazone (six deaths) compared with metformin monotherapy (one death). Removal of any one study did not impact substantially the effect size or confidence interval of the combined estimate. The pooled risk difference for the combination of metformin plus rosiglitazone versus metformin monotherapy was 0.3% (95% CI, -0.1 to 0.8%). (SOE for short-term mortality: Low; Metformin monotherapy favored over combination of metformin plus rosiglitazone)

Figure 42. Pooled odds ratio of short-term all-cause mortality comparing metformin with a combination of metformin plus rosiglitazone



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus rosiglitazone; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

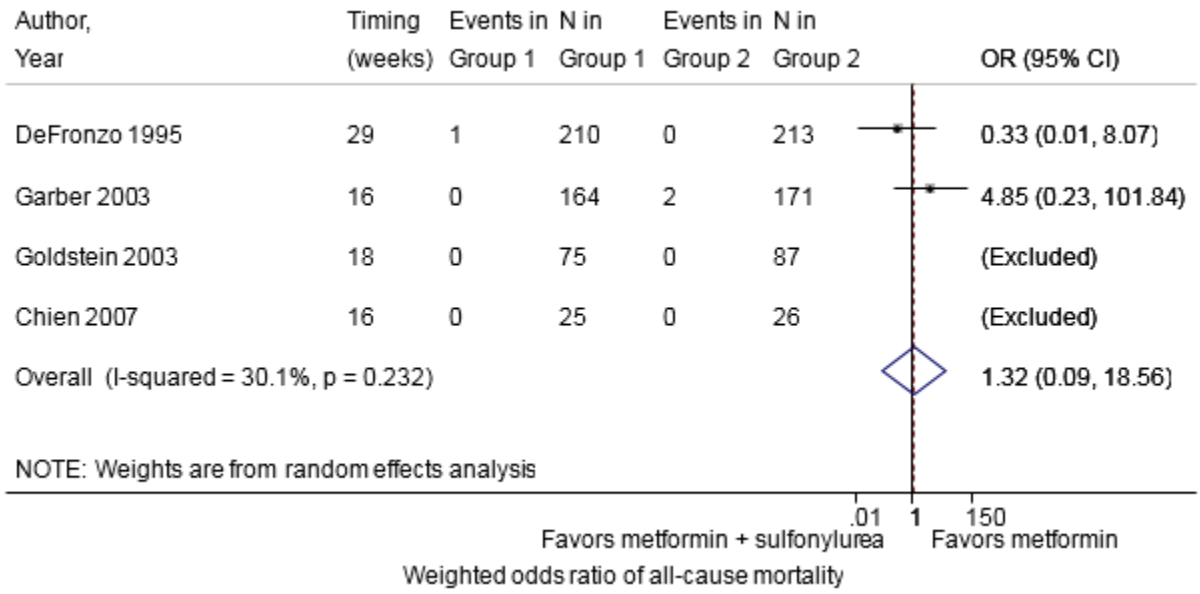
A single 24-week RCT compared the effects of metformin (n=103) to metformin plus pioglitazone (n=110) reported on all-cause mortality; no deaths occurred in either arm.[125] (SOE: Insufficient for combination of metformin plus pioglitazone)

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

Five RCTs, each ranging from 16 to 104 weeks, compared the effects of metformin with the combination of metformin plus a sulfonylurea on all-cause mortality.[129, 130, 137, 138, 141] In the one long-term study, all-cause mortality was similar in the metformin (1/101, 1%) and metformin plus sulfonylurea (3/307, 1%) arms at 104 weeks; losses to followup were >30% in these arms.[141]

For the four short-term studies (16 to 29 weeks of followup), there were only three deaths and no significant difference for metformin plus a sulfonylurea versus metformin (pooled OR, 1.32; 95% CI, 0.09 to 18.56; $I^2 = 30.1\%$) (Figure 43). Although removal of one study did change the direction of the combined estimate (pooled OR, 0.33),[129] removal of a single study did not substantially change the width of the confidence interval. The pooled risk difference for the combination of metformin plus a sulfonylurea compared with metformin monotherapy was 0.0% (95% CI, -1.0 to 1.0%). (SOE: Low; Neither treatment favored)

Figure 43. Pooled odds ratio of short-term all-cause mortality comparing metformin with a combination of metformin plus a sulfonylurea



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sulfonylurea; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

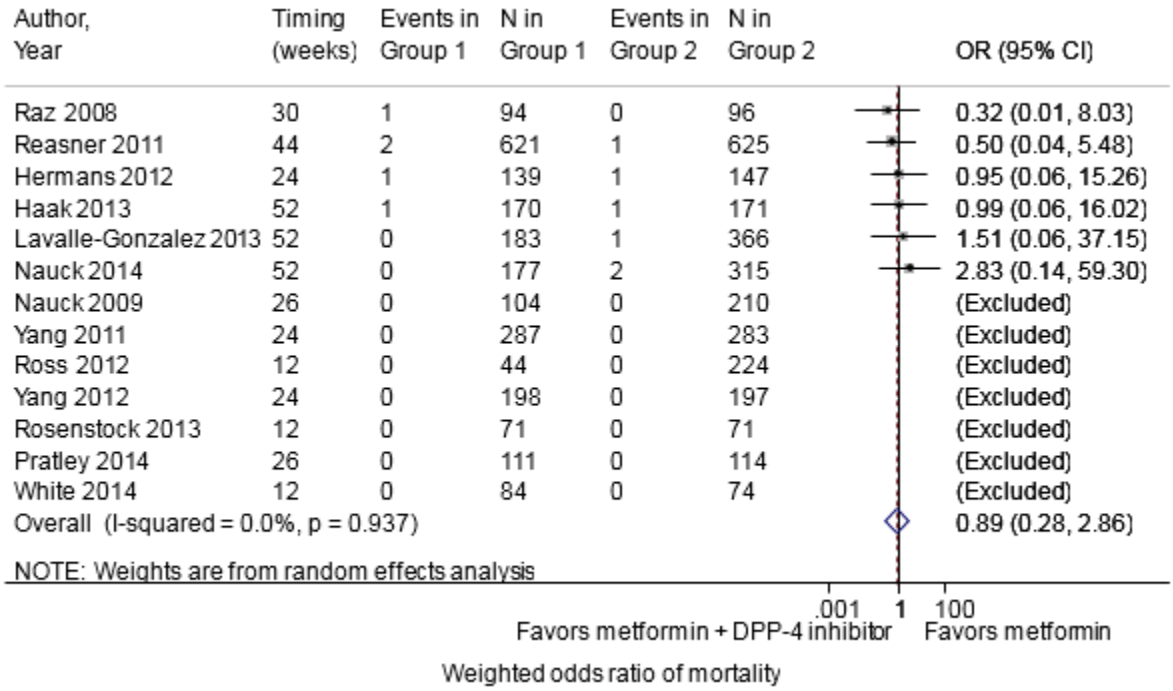
Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Seventeen RCTs (published in 18 articles) comparing metformin plus a DPP-4 inhibitor to metformin monotherapy reported on all-cause mortality.[84-87, 141, 142, 145, 146, 148, 149, 151-154, 158, 159, 161, 164]

Three RCTs longer than one year (78 to 104 weeks) were not meta-analyzed because of differences in dosing of metformin in the maximally-dosed DPP-4 inhibitor arms.[85, 87, 141] Mortality rates were low and did not differ by more than ~0.5 absolute percentage points between metformin and metformin plus DPP-4 inhibitor arms; the dose of medication did not appear to significantly affect results (Table 23).[85, 87, 141] Losses to followup ranged from 20 to 48 percent across the arms of these studies.

For studies 52 weeks or less, the pooled OR indicated no difference in mortality rates for metformin plus DPP-4 inhibitor versus metformin (pooled OR, 0.89; 95% CI, 0.28 to 2.86) (Figure 44).[84, 86, 142, 145, 146, 148, 151-154, 158, 159, 161, 164] We did not find statistical heterogeneity (I^2 = 0.0%). Removal of any one study did not change the direction of effect or inference, and there was no evidence of publication bias statistically (P = 0.80) using Harbord's modified test. Three studies did not report on event rates in the metformin arm, and we imputed "0" events for these studies.[146, 158, 159] The pooled risk difference for the combination of metformin plus a DPP-4 inhibitor compared with metformin monotherapy for short-term mortality was -0.0% (95% CI, -0.3 to 0.3%).

Figure 44. Pooled odds ratio for short-term all-cause mortality comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

Four RCTs included additional arms, with lower doses than the arms included in the meta-analysis. Results from these arms did not differ from those of the meta-analysis (Table 23).[84, 86, 154, 164] We excluded one of the short-term RCTs from the meta-analysis because it underdosed the study drugs substantially; that 12-week study reported no deaths in either arm (Table 23).[149] (SOE: Low; Neither favored for short-term mortality)

Table 23. Randomized controlled trials or arms of randomized controlled trials excluded from the meta-analysis comparing metformin with a combination of metformin plus a DPP-4 inhibitor on all-cause mortality

Author, Year	Followup (Weeks)	Metformin Dose in Monotherapy Arm	Metformin Dose in Combination Arm	DPP-4 Inhibitor Dose in Combination Arm	Number of Deaths / N (%) in Metformin Arm	Number of Deaths / N (%) in Metformin + DPP-4 Inhibitor Arm
Kadowaki, 2013[149]	12	96% of participants on ≤750mg	94% of participants on ≤750mg	Sitagliptin 50 mg	0/72 (0)	0/77 (0)
Pratley, 2014[84]	26	1000 mg	1000 mg	Alogliptin 25 mg	0/109 (0)	0/106 (0)
		1000 mg	2000 mg	Alogliptin 25 mg	0/109 (0)	0/114 (0)
		2000 mg	1000 mg	Alogliptin 25 mg	0/111 (0)	0/106 (0)
		2000 mg*	2000 mg	Alogliptin 25 mg	0/111 (0)	0/114 (0)
Haak, 2013[164]	52	2000 mg	1000 mg	Linagliptin 5 mg	1/170 (0.6)	2/225 (0.9)
		2000 mg*	2000 mg	Linagliptin 5 mg	1/170 (0.6)	1/171 (0.6)
Haak, 2012[86]	24	1000 mg	1000 mg	Linagliptin 5 mg	0/144 (0)	0/143 (0)
		1000 mg	2000 mg	Linagliptin 5 mg	0/144 (0)	0/143 (0)
		2000 mg	1000 mg	Linagliptin 5 mg	1/147 (0.7)	0/143 (0)
		2000 mg	2000 mg	Linagliptin 5 mg	1/147 (0.7)	0/143 (0)
Nauck, 2009[154]	26	Mean 1868 mg	Mean 1837 mg	Alogliptin 12.5 mg	0/104 (0)	1/213 (0.5)
		Mean 1868 mg*	Mean 1846 mg	Alogliptin 25 mg	0/104 (0)	0/210 (0)
Pfutzner, 2011[87]	76	2000 mg	2000 mg	Saxagliptin 5 mg	5/328 (1.5)	1/320 (0.3)
		2000 mg	2000 mg	Saxagliptin 10 mg	5/328 (1.5)	2/323 (0.6)
Williams-Herman, 2010[85]	104	2000 mg	1000 mg	Sitagliptin 100 mg	2/176 (1.1)	1/190 (0.6)
		1000 mg	1000 mg	Sitagliptin 100 mg	1/182 (0.5)	1/190 (0.6)
		1000 mg	2000 mg	Sitagliptin 100 mg	1/182 (0.5)	1/182 (0.5)
		2000 mg	1000 mg	Sitagliptin 100 mg	0/182 (0)	1/190 (0.6)
		2000 mg	2000 mg	Sitagliptin 100 mg	0/182 (0)	1/182 (0.5)
Ahren, 2014[141]	104	≥1500 mg	≥1500 mg	Sitagliptin 100 mg	1/101 (1)	1/302 (0.3)

DPP-4 = dipeptidyl peptidase-4; mg = milligrams
*arm included in the meta-analysis

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

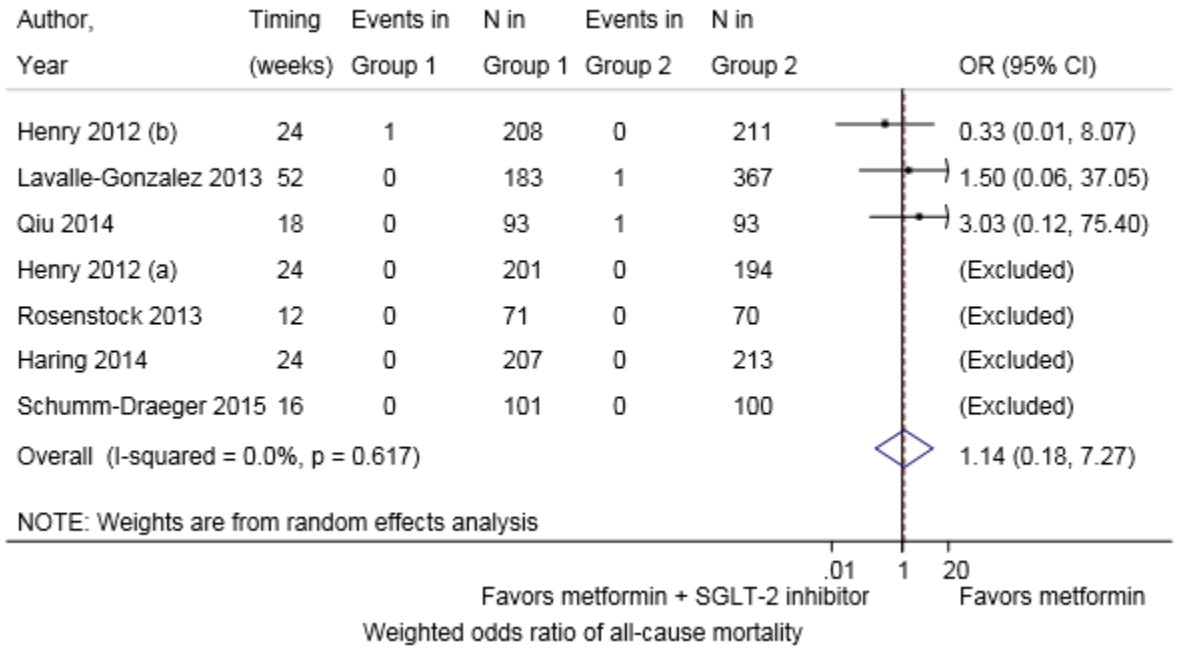
Nine RCTs (in eight articles) compared metformin monotherapy with metformin plus an SGLT-2 inhibitor and reported on mortality (five deaths).[88, 153, 158, 165, 166, 168-170]

Two of the RCTs were long-term (102 weeks) and reported low rates of mortality across arms (one death in metformin arm in one study and one death in metformin plus SGLT-2 inhibitor arm in the other).[169, 170] Losses to follow up were >20% across the arms of these studies.[169, 170]

Six of these studies were short (duration range, 12 to 24 weeks), including two trials described by Henry, et al;[88] there was no difference in mortality between arms. The combined OR for all-cause mortality for metformin plus SGLT-2 inhibitor versus metformin was 1.14

(95% CI, 0.18 to 7.27) (Figure 45).[88, 153, 158, 165, 166, 168] We did not find statistical heterogeneity (I^2 = 0.0%). Removal of any one study did not change the overall inference. Two of these RCTs did not report on events in the metformin arm, and we imputed "0" events in these arms.[165, 166] The pooled risk difference for the combination of metformin plus a SGLT-2 inhibitor compared with metformin monotherapy for short-term mortality was 0.0% (95% CI, -0.5 to 0.5%).

Figure 45. Pooled odds ratio for short-term all-cause mortality comparing metformin with a combination of metformin plus an SGLT-2 inhibitor, stratified by study duration



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

Six of the nine RCTs comparing metformin with metformin plus a SGLT-2 inhibitor had multiple different dosing arms; event rates were low and did not appear to vary by dose.[153, 158, 165, 166, 168, 170] (SOE: Low: Neither favored for short-term mortality; SOE: Low: Neither favored for long-term mortality)

Metformin Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Two RCTs compared metformin with the combination of metformin plus a GLP-1 receptor agonist. In the 52-week study, no deaths were reported in the metformin monotherapy arm (0/177, 0%); one death was reported in the metformin plus dulaglutide 1.5 mg weekly arm (1/304, 0.3%); and no deaths were observed in the dulaglutide 0.75 mg weekly arm (0/302, 0%) over 52 weeks.[159] In a longer RCT, with 104 weeks of followup, one death in the metformin arm (1/101, 1%), and three deaths (3/302, 1%) in the metformin plus albiglutide arm were reported.[141] (SOE: Low; Neither treatment favored)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Two multinational RCTs[175, 177] directly compared the effect of the combination of metformin plus rosiglitazone with the combination of metformin plus a sulfonylurea. One study (N=596) reported two deaths in each arm (2/294, 0.7% in the rosiglitazone arm and 2/301, 0.7% in the sulfonylurea arm) over 52 weeks of treatment,[175] and the other reported a fatal myocardial infarction in the metformin plus rosiglitazone arm (1/204, 0.5%) and no deaths in the metformin plus sulfonylurea arm (N=514) at 32 weeks.[177]

A single retrospective observational study of 80,936 patients with both Veterans Health Administration and Medicare coverage between 2000 and 2009 (minimum follow up, 12 month; mean followup, not reported) reported an increased mortality risk for patients taking the combination of metformin plus a sulfonylurea for at least 1 year compared with those on the combination of metformin plus a thiazolidinedione: adjusted HR, 1.5; 95% CI, 1.09 to 2.09; p=0.014.[242] (SOE: Low; Neither metformin plus rosiglitazone nor metformin plus a sulfonylurea favored for short-term mortality)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a DPP-4 Inhibitor

A single RCT compared the combination of metformin plus pioglitazone with the combination of metformin plus sitagliptin and reported one death in the metformin plus sitagliptin arm (1/172, 0.6%) and did not report on deaths in the metformin plus pioglitazone arm (n=172) at 26 weeks.[188] (SOE: Insufficient)

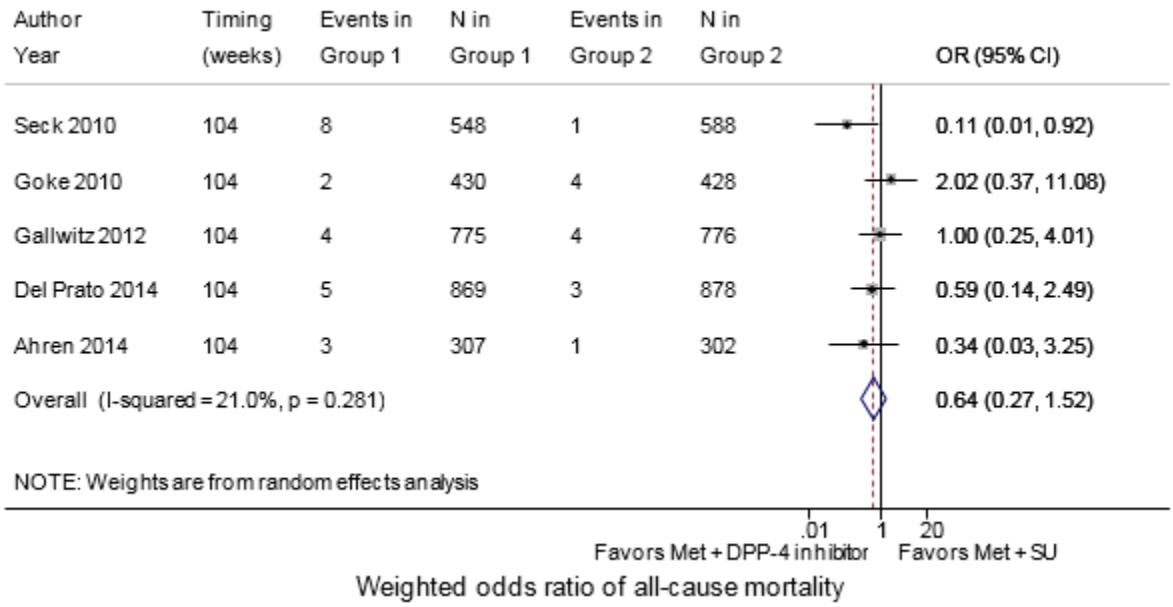
Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

A single RCT compared the combination of metformin plus pioglitazone (n=172) with the combination of metformin plus weekly exenatide (n=170) at 26 weeks but only provided data on deaths in a third arm (metformin plus sitagliptin).[188] Given the reporting in the metformin plus sitagliptin arm, we may infer that there were no deaths in the metformin plus pioglitazone and metformin plus exenatide arms, but this information was not reported.[188] (SOE: Insufficient)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Five RCTs compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a DPP-4 inhibitor and reported on mortality at 104 weeks.[194-197] The pooled OR for metformin plus a DPP-4 inhibitor versus metformin plus a sulfonylurea at 2 years was 0.64 (95% CI, 0.27 to 1.51) (Figure 46).[141, 194-197] We did not find evidence of substantial statistical heterogeneity (I^2 = 21%). The pooled risk difference for the combination of metformin plus a DPP-4 inhibitor compared with the combination of metformin plus a sulfonylurea was -0.3% (95% CI, -0.8 to 0.2%).

Figure 46. Pooled odds ratio for long-term all-cause mortality comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; Met = metformin; OR = odds ratio; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Two additional RCTs evaluated this comparison but were not included in the meta-analysis because of their shorter durations.[190, 193] One trial with 52 weeks of followup conducted among persons (predominantly men) greater than 65 years of age reported one death in each arm (1/360 (0.3%) in the metformin plus sulfonylurea arm; 1/360 (0.3%) in the metformin plus saxagliptin arm).[193] The other trial had 30 weeks of followup and reported one death in the metformin plus sulfonylurea arm (1/519, 0.2%) and no deaths in the metformin plus sitagliptin arm (0/516, 0%).[190]

A single retrospective cohort study in the Danish National Registry reported a significantly decreased risk of death among metformin plus DPP-4 inhibitor users (n=11,138) versus metformin plus sulfonylurea users (n=25,092) with median follow up of 2.1 years (adjusted rate ratio, 0.65; 95% CI, 0.54 to 0.8).[227] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored for long-term mortality; SOE: Insufficient for short-term mortality)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

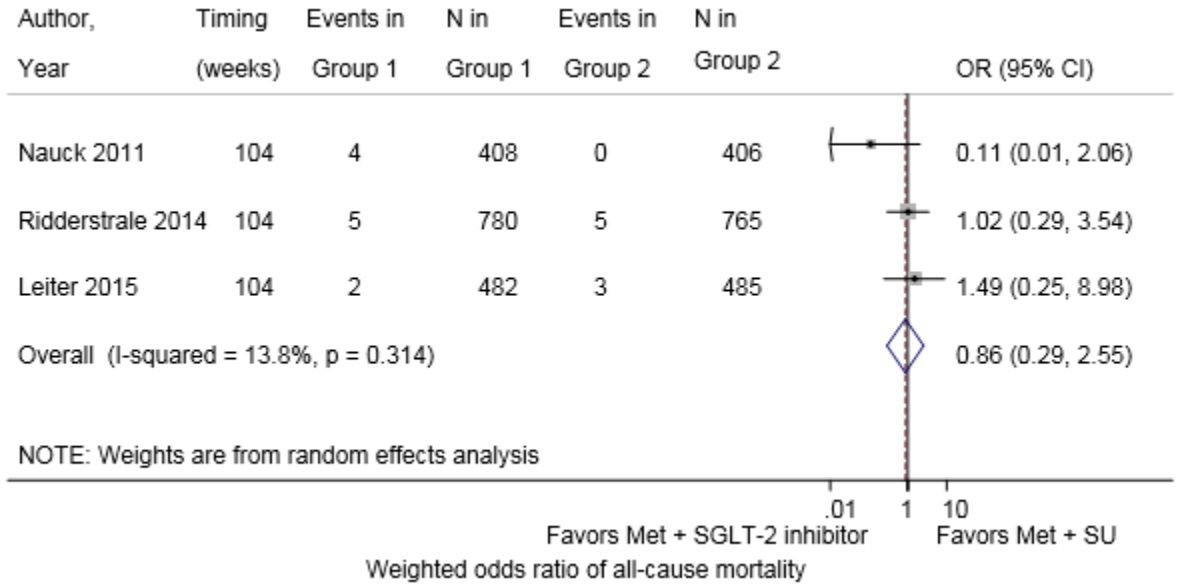
Three long-term RCTs (reported in four publications), each with a duration of 104 to 208 weeks, reported on all-cause mortality for this comparison.[54, 199-201] Mortality rates were low across the studies.

An extension of Nauck 2011, with extremely high losses to followup, reported a higher rate of mortality in the metformin plus sulfonylurea (5/408, 1.2%) versus metformin plus SGLT-2 inhibitor (2/406, 0.5%) arm at 208 weeks.[54]

Meta-analysis of the data from these trials at 104 weeks suggested that long-term all-cause mortality [which was low (<1%) across studies] was similar for metformin plus SGLT-2

inhibitors and metformin plus sulfonylurea (pooled OR, 0.86; 95% CI, 0.29 to 2.55) (Figure 47).[199-201] We did not find statistical heterogeneity (I^2 = 14%), and removal of any one study did not change the inference of no difference between arms. The pooled risk difference for the combination of metformin plus an SGLT-2 inhibitor compared with metformin plus a sulfonylurea was -0.2% (95% CI, -0.8 to 0.5%). One of the RCTs evaluated metformin plus canagliflozin at 100 mg daily (versus 300 mg daily, which was included in the meta-analysis); mortality was the same as in the 300 mg arm (3/483, 0.6%).[201] Of note, two[200, 201] of three studies did not use an intention-to-treat approach and had large losses to followup across arms. (SOE: Low; Neither favored for long-term mortality)

Figure 47. Pooled odds ratio for long-term all-cause mortality comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = metformin plus a sodium-glucose co-transporter-2 inhibitor; Met = metformin; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Two RCTs with more than two years of followup reported similar mortality rates for the combination of metformin plus a sulfonylurea compared to metformin plus a GLP-1 receptor agonist (Table 24).[53, 141]

Table 24. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a GLP-1 receptor agonist on all-cause mortality

Author, Year	Followup	Number of Deaths/N (%) in the Metformin + Sulfonylurea Arm	Number of Deaths/N (%) in the Metformin + GLP-1 Receptor Agonist Arm
Ahren, 2014[141]	104 weeks	Glimepiride 3.1 mg: 3/307 (1.0)	Albiglutide 40.5 mg: 3/302 (1.0)
Gallwitz, 2012[53]	48 months (assumed)	Glimepiride 2.0mg: 5/508 (1.0)	Exenatide 17.4 mg: 5/510 (1.0)

GLP-1 = glucagon-like peptide-1; mg = milligrams; mean daily dose shown for glimepiride and exenatide; mean weekly dose shown for albiglutide

A single retrospective cohort study in the Danish National Registry did not find a significantly decreased risk of death among metformin plus GLP-1 receptor agonist users (n=4,345) versus metformin plus sulfonylurea users (n=25,092) over a median follow up of 2.1 years (adjusted rate ratio, 0.77; 95% CI, 0.51 to 1.17).[227] (SOE: Low; Neither favored for long-term mortality)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a Basal Insulin

A single retrospective cohort study in the Danish National Registry found a significantly increased risk of death among metformin plus basal insulin users (n=6,858) versus metformin plus sulfonylurea users (n=25,092) over median follow up of 2.1 years (adjusted rate ratio, 1.95; 95% CI, 1.7 to 2.25).[227] (Not graded)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a Premixed Insulin

Two multinational RCTs (N=938) compared the effect of the combination of metformin plus a sulfonylurea with the combination of metformin plus a premixed insulin (insulin aspart 70/30 in one study and insulin lispro 75/25 in the other). Each trial reported one death in the metformin plus premixed insulin arms (1/108 (1%) in one study[208] and 1/296 (0.3%) in the second study[207]) and no deaths in the metformin plus sulfonylurea arms at 16 weeks.[207, 208] (SOE: Low; Combination of metformin plus a sulfonylurea favored for short-term mortality)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Two RCTs compared metformin plus sitagliptin with metformin plus a SGLT-2 inhibitor and reported on mortality.[153, 158] A small (N=212) 12-week trial reported no deaths in any arm (metformin plus sitagliptin, metformin plus empagliflozin 10 mg, and metformin plus empagliflozin 25 mg).[153] A second trial with 52 weeks of followup reported one death in the metformin plus sitagliptin arm (1/366, 0.3%), one death in the metformin plus canagliflozin 300 mg arm (1/367, 0.3%), and no deaths in the metformin plus canagliflozin 100 mg arm (0/368, 0%).[158] (SOE: Low; Neither favored for short-term mortality)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Three RCTs compared the combination of metformin plus sitagliptin with metformin plus a GLP-1 receptor agonist (Table 25). In the study with the longest followup (104 weeks), mortality was higher in the metformin plus GLP-1 receptor agonist arm;[141] however, the shorter study (52 weeks) reporting on mortality in both arms reported a higher death rate in the metformin plus DPP-4 inhibitor arm.[159] (SOE: Insufficient)

Table 25. Randomized controlled trials comparing a combination of metformin plus sitagliptin with a combination of metformin plus a GLP-1 receptor agonist on all-cause mortality

Author, Year	Followup	Number of Deaths/N (%) in the Metformin + Sitagliptin Arm	Number of Deaths/N (%) in the Metformin + GLP-1 Receptor Agonist Arm
Ahren, 2014[141]	104 weeks	1/302 (0.3)	3/302 (1.0)
Nauck, 2014[159]	26 weeks	0/315 (0)	Dulaglutide 0.75 mg: 0/302 (0) Dulaglutide 1.5 mg: 0/304 (0)
	52 weeks	2/315 (0.6)	Dulaglutide 0.75 mg: 0/302 (0) Dulaglutide 1.5 mg: 1/304 (0.3)
Bergenstal, 2010[188]	26 weeks	1/172 (0.6)	Exenatide 2 mg weekly: NR/170

GLP-1 = glucagon-like peptide-1; mg = milligrams; NR = not reported

Combination of Metformin Plus a GLP-1 Receptor Agonist Versus a Combination of Metformin Plus a Basal Insulin

A single RCT (N=321) compared metformin plus exenatide with metformin plus insulin glargine and reported no deaths in either arm at 26 weeks.[212] (SOE: Insufficient)

Strength of Evidence for All-Cause Mortality

We found low or insufficient strength of evidence for all comparisons evaluating all-cause mortality (see Key Points, Table 26, Table 27, and Table 28).

Most evidence on this outcome came from RCTs lasting less than 2 years that we found to be at low or medium risk of bias. None of the RCTs were designed to evaluate all-cause mortality. Observational studies had medium risk of bias and tended to support RCT findings. Evidence was more consistent across monotherapy comparisons, with less consistency for combination therapy comparisons, in part because of the smaller number of studies for these comparisons. The RCT evidence on mortality was substantially underpowered and imprecise because of few studies and small sample sizes with few events. As a result, we could not exclude short-term harm for any comparison with moderate strength of evidence.

Our evaluation of publication bias was generally limited by the small number of studies. We found unpublished studies that may have affected our grading of the evidence. Published studies suggested a decrease in long-term mortality for metformin plus a DPP-4 inhibitor versus metformin plus a sulfonylurea; one unpublished study was consistent with these conclusions. The single published RCT suggested increased short-term mortality for sulfonylureas versus DPP-4 inhibitors; two unpublished RCTs confirmed those findings. For the comparison of metformin versus metformin plus a sulfonylurea, we only identified one poor-quality, long-term study which showed similar mortality at 104 weeks across arms; however, an unpublished study suggested an increased risk of long-term all-cause mortality for metformin plus a sulfonylurea. For the comparison of metformin versus metformin plus a GLP-1 receptor agonist, we also only identified a single long-term study which suggested similar mortality rates at 104 weeks; however, an unpublished trial found more deaths in the metformin plus GLP-1 receptor agonist arm compared with the metformin monotherapy arm.

Table 26. Strength of evidence domains for monotherapy comparisons in terms of all-cause mortality among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. pioglitazone	RCTs: 4 (1755) Obs: 1 (NR)	Low Medium	Consistent Unknown	Direct Direct	Imprecise N/A	Undetected N/A	Low	Neither treatment favored for short-term mortality
Metformin vs. rosiglitazone	RCTs: 2 (3224) Obs: 2 (193,172)	High Medium	Inconsistent Consistent	Direct Direct	Imprecise Precise	Undetected N/A	Low	Metformin favored
Metformin vs. SU (shorter duration studies)	RCTs: 4 (928)	Low	Inconsistent	Direct Direct	Imprecise Imprecise	Undetected N/A	Low	Neither favored for short-term mortality
Metformin vs. SU (longer duration studies)	RCTs: 2 (3199) Obs: 7 (398,227)	Medium Medium	Consistent Consistent	Direct Direct	Imprecise Precise	Undetected N/A	Low	Metformin favored for long-term mortality
Metformin vs. DPP-4 inhibitors	RCTs: 5 (4,792) Obs: 1 (84,756)	Low Medium	Consistent Unknown	Direct Direct	Imprecise Imprecise	Undetected N/A	Low	Neither treatment favored for short-term mortality
Metformin vs. SGLT-2 inhibitors	RCTs: 4 (2,041)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. GLP-1 receptor agonists	RCTs: 2 (820)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored Incomplete reporting on death
Rosiglitazone vs. SU	RCTs: 2 (3,484) Obs: 2 (79,681)	Medium Medium	Inconsistent Consistent	Direct Direct	Imprecise Precise	Undetected N/A	Insufficient	Unable to determine
Pioglitazone vs. SU	RCT: 1 (502) Obs: 1 (20,450)	Low Medium	Unknown Unknown	Direct Direct	Imprecise Precise	Undetected N/A	Insufficient	Unable to determine

Table 26. Strength of evidence domains for monotherapy comparisons in terms of all-cause mortality among adults with type 2 diabetes (continued)

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Pioglitazone vs. DPP-4 inhibitors	RCTs: 2 (1031)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
SU vs. DPP-4 inhibitors	RCT: 1 (426)	Medium	Unknown	Direct	Imprecise	Undetected	Low	DPP-4 inhibitors favored for short-term mortality
SU vs. GLP-1 receptor agonists	RCTs: 2 (1157)	High	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine Insufficient reporting of events
DPP-4 inhibitors vs. SGLT-2 inhibitors	RCTs: 2 (1486)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
DPP-4 inhibitors vs. GLP-1 receptor agonists	RCT: 1 (820)	Medium	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; Met = metformin; Obs = observational; RCT = randomized controlled trial; RD = risk difference; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95% confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Table 27. Strength of evidence domains for metformin versus metformin-based combination comparisons in terms of all-cause mortality among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + pio	RCT: 1 (213)	Low	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. metformin + rosiglitazone	RCTs: 7 (3242)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin monotherapy favored
Metformin vs. metformin + SU	RCTs: 5 (1983)	Medium	Consistent	Direct	Imprecise	Suspected‡	Low	Neither treatment favored for short-term mortality
Metformin vs. metformin + DPP-4 inhibitors (<2 years)	RCTs: 18 (12,446)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored for short-term mortality
Metformin vs. metformin + DPP-4 inhibitors (long duration studies)	RCTs: 2 (2140)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. metformin + SGLT-2 inhibitors (short duration studies)	RCTs: 7 (4340)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored for short-term mortality
Metformin vs. metformin + SGLT-2 inhibitors (long duration studies)	RCTs: 2 (728)	High	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. metformin + GLP-1 receptor agonists	RCT: 2 (2110)	Medium	Consistent	Direct	Imprecise	Suspected	Low	Neither treatment favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; pio = pioglitazone; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95% confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

‡ We identified one long-term study showing five deaths in the sulfonylurea arm and one death in the metformin arm at 156 weeks.

Table 28. Strength of evidence domains for metformin-based combination comparisons in terms of all-cause mortality among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + rosiglitazone vs. metformin + SU	RCTs: 2 (1110) Obs: 1 (80,936)	Low Medium	Consistent Unknown	Direct Direct	Imprecise Precise	Undetected N/A	Low	Neither treatment favored for short-term mortality
Metformin + pioglitazone vs. metformin + DPP-4 inhibitors	RCT: 1 (514)	Low	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + pioglitazone vs. metformin + GLP-1 receptor agonists	RCT: 1 (514)	Low	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + SU vs. metformin + DPP-4 inhibitors (longer duration studies)	RCTs: 5 (6693) Obs: 1 (47,433)	Medium Medium	Consistent Unknown	Direct Direct	Imprecise Precise	Undetected N/A	Low	Metformin + DPP-4 inhibitors favored for long-term mortality
Metformin + SU vs. metformin + DPP-4 inhibitors (shorter duration studies)	RCTs: 2 (1755)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration studies)	RCTs: 3 (3815)	High	Inconsistent	Direct	Imprecise	Undetected	Low	Neither treatment favored for long-term mortality
Metformin + SU vs. metformin + GLP-1 receptor agonists	RCT: 2 (1678) Obs: 1 (29,437)	High Medium	Consistent Unknown	Direct Direct	Imprecise Precise	Undetected N/A	Low	Neither treatment favored for long-term mortality
Metformin + SU vs. metformin + premixed insulin	RCTs: 2 (938)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin + SU favored for short-term mortality

Table 28. Strength of evidence domains for metformin-based combination comparisons in terms of all-cause mortality among adults with type 2 diabetes (continued)

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	RCTs: 2 (1779)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored for short-term mortality
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 receptor agonists	RCTs: 3 (2216)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine Insufficient reporting of events in all arms
Metformin + GLP-1 receptor agonists vs. metformin + basal insulin	RCT: 1 (321)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; Met = metformin; Obs = observational; pio = pioglitazone; RCT = randomized controlled trial; RD = absolute risk difference; rosi = rosiglitazone; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short-term (1 year or shorter) due to the few longer duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95% confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Cardiovascular Mortality

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Three RCTs compared metformin with thiazolidinediones and did not find differences in cardiovascular mortality.[50, 63, 70] Two of the RCTs were small, lasted less than one year, and did not report any cardiovascular deaths (Table 29).[63, 70] Studies were not combined because of different lengths of followup and different thiazolidinediones under study. ADOPT was the single long-term RCT (median followup of 4.0 years): the actual number of participants for which ADOPT ascertained CVD mortality is unclear and withdrawals were high across the arms [37% (rosiglitazone) and 38% (metformin)].[50] (SOE: Low; Neither favored)

Table 29. Randomized controlled trials comparing metformin with thiazolidinediones on cardiovascular mortality

Author, Year	Followup	Number of Events/N (%) in the Metformin Arm	Number of Events/N (%) in the Thiazolidinedione Arm
Lawrence, 2004[63]	24 weeks	0/20 (0%)	0/20 (pioglitazone) (0%)
Erem, 2014[70]	48 weeks	0/19 (0%)	0/19 (pioglitazone) (0%)
Kahn, 2006[50]	4 years (median)	2/1454 (0.1%)	1/1456 (0.1%) (rosiglitazone)

Metformin Versus Sulfonylureas

Two high-quality RCTs compared metformin with sulfonylureas and reported on cardiovascular mortality.[50, 231] ADOPT, conducted among patients with newly diagnosed and untreated diabetes (N=2895), reported a slightly higher incidence of fatal MI in the glyburide (3/1441, 0.2%) versus the metformin (2/1454, 0.1%) arm (glyburide vs. metformin: calculated RR, 1.5 (95% CI, 0.3 to 9.0); calculated between-group difference, 0.1%). Median followup was 4.0 years for the metformin (maximum dose 2,000 mg; mean dose not reported) arm and 3.3 years for the glyburide (maximum dose 15 mg; mean dose not reported) arm, and losses to followup were also differential for the metformin (38%) arm vs. the glyburide (44%) arm.[50] The smaller RCT was conducted in China among patients with known coronary heart disease (clinical evidence of acute MI or coronary stenosis >50% on angiogram) and also reported a higher risk of cardiovascular mortality in the sulfonylurea (glipizide, mean dose 28.3 mg) arm (11/148, 7.4%) compared with the metformin (mean dose 1,400 mg) arm (7/156, 4.5%) over 2.8 years.[231] We calculated the RR of cardiovascular mortality comparing sulfonylurea with metformin to be 1.66 (95% CI, 0.66 to 4.16) and the between-group difference to be 2.9 percent. Losses to followup were 21 percent for each arm of this trial.[231] Losses to follow up were the same (20%) across arms in Hong et al.,[231] decreasing the risk of non-conservative bias due to losses of follow up across arms. In ADOPT, given differential losses to followup and followup duration across arms, study results were likely biased to the null, lending further support to the inference that metformin was favored over sulfonylurea monotherapy.

Three retrospective cohort studies, analyzing two cohorts compared metformin with a sulfonylurea, and all found a higher risk of cardiovascular mortality for sulfonylurea users versus metformin users (Table 30).[225, 229, 230] To account for confounding, two of these studies used propensity score matching,[225, 229] and one used multivariate regression.[230] (SOE: Moderate; Metformin favored for long-term CVD mortality)

Table 30. Observational studies comparing metformin with sulfonylureas on cardiovascular mortality

Author, Year	Cohort	Metformin, N	Sulfonylurea, N	Median Followup	Adjusted HR (95% CI) for Cardiovascular Mortality
Johnson, 2005[230]	Saskatchewan Health database	923	2138	4.6 to 5.6 years	0.76 (0.58 to 1.00) Reference: sulfonylurea
Schramm, 2011[229]	Danish National Patient Register	Prior MI 2,906 No prior MI 43,340	Prior MI Glibenclamide: 1,168 Glipizide: 660 Glimepiride: 3,894 No prior MI Glibenclamide: 12,495 Glipizide: 6,965 Glimepiride: 36,313	3.3 years	Prior MI Glibenclamide: 1.5 (1.22 to 1.84) Glipizide: 1.63 (1.28 to 2.07) Glimepiride: 1.32 (1.11 to 1.57) No prior MI Glibenclamide: 1.14 (1.03 to 1.25) Glipizide: 1.25 (1.12 to 1.4) Glimepiride: 1.28 (1.18 to 1.38) Reference: metformin
Andersson, 2010[225]	Danish National Patient Register – Incident admission for heart failure*	688	3615	844 days	0.79 (0.65 to 0.96) Reference: sulfonylurea

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction
* Unclear if this population was included in Schramm, 2011[229]

Metformin Versus DPP-4 Inhibitors

Three RCTs compared metformin with DPP-4 inhibitors and reported on cardiovascular mortality (Table 31). These studies varied in duration and did not use similar definitions for cardiovascular events. Therefore, we did not combine them in a meta-analysis. Cardiovascular mortality was rare and appeared to be more frequent in the metformin than DPP-4 inhibitor arms, when reported.[85-87] The longest study reported no cardiovascular mortality in either arm.[85] (SOE: Low; DPP-4 inhibitors favored)

Table 31. Randomized controlled trials comparing metformin with DPP-4 inhibitors on cardiovascular mortality

Author, Year	Outcome	Followup (Weeks)	Metformin Dose: Number of Events/N (%)	DPP-4 Inhibitor Dose: Number of Events/N (%)
Haak, 2012[86]	Fatal MI	24	1000 mg: 0/142 (0.0%) 2000 mg: 1/147 (0.7%)	Linagliptin 5 mg: 0/142 (0.0%)
Pfutzner, 2011[87]	Sudden death, cardiac arrest, coronary arteriosclerosis, cardiac failure, acute MI	76	2000 mg: 3/328 (0.9%)	Saxagliptin 10 mg: 1/335 (0.3%)
Williams-Herman, 2010[85]	Sudden cardiac death or worsening CHD	104	1000 mg: 0/182 2000 mg: 0/182	Sitagliptin 100 mg: 0/179

CHD = coronary heart disease; DPP-4 = dipeptidyl peptidase-4; mg = milligrams; MI = myocardial infarction

Thiazolidinediones Versus Sulfonylureas

The ADOPT trial compared rosiglitazone with glyburide and reported two fatal myocardial infarctions in the rosiglitazone arm (2/1446, 0.1%) and three fatal myocardial infarctions in the glyburide arm (3/1441, 0.2%) resulting in a calculated risk ratio of 0.66 (95% CI, 0.11 to 3.97) and between-group difference of -0.1% for rosiglitazone versus glyburide. Notably, losses to followup and followup duration were differential across the arms; losses to followup were higher (44% vs. 37%) for the sulfonylurea versus rosiglitazone arm and median followup was shorter (3.3 years vs. 4.0 years) for the sulfonylurea versus rosiglitazone arm.[50] (SOE: Low; Rosiglitazone favored for long-term CVD mortality)

Sulfonylureas Versus DPP-4 Inhibitors

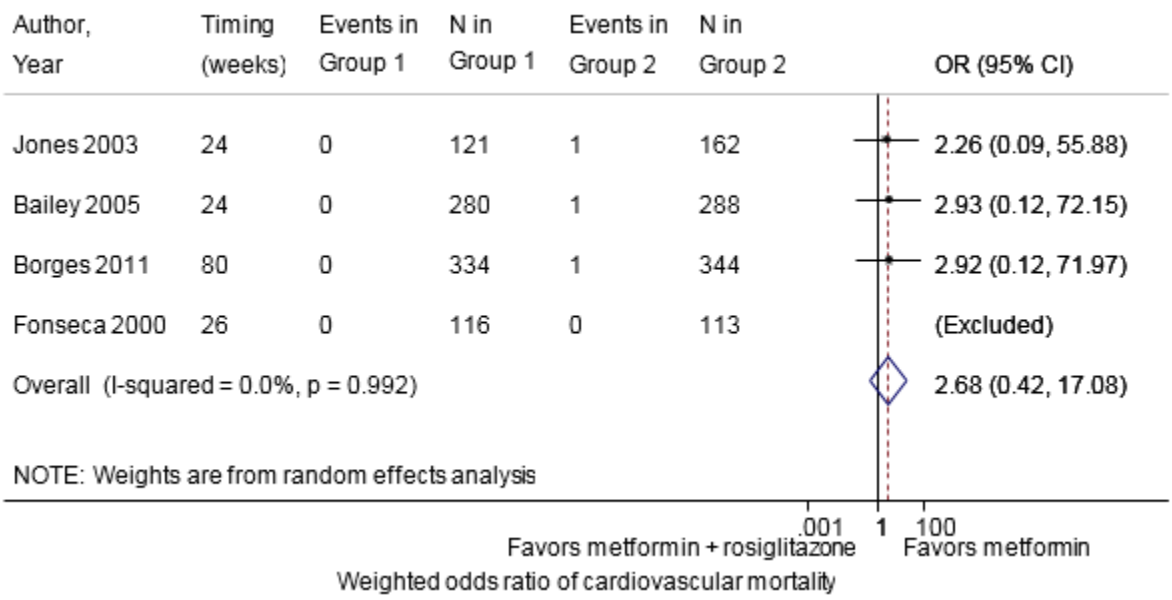
Two small RCTs compared a sulfonylurea with a DPP-4 inhibitor (duration 52 to 58 weeks) and reported mixed results on fatal myocardial infarction.[106, 107] The high-quality study reported one fatal myocardial infarction in the linagliptin arm (1/151, 0.7%) and none in the sulfonylurea arm (0/151, 0%),[106] and the other study reported two events in the sulfonylurea arm (2/212, 0.9%) and did not report on fatal myocardial infarctions in the sitagliptin arm (n=211).[107] The lower-quality study did not use an intention-to-treat analysis for fatal myocardial infarction and had large losses to followup (19.8% and 22.3% in the sulfonylurea and DPP-4 inhibitor arms, respectively).[107] (SOE: Insufficient)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Five RCTs reported in four articles[120, 123, 127, 241] compared metformin with metformin plus rosiglitazone and found non-significantly increased odds of short-term cardiovascular mortality for the combination of metformin plus rosiglitazone versus metformin monotherapy (pooled OR, 2.68; 95% CI, 0.42 to 17.08) (Figure 48). Three of the studies reported a single cardiovascular death in the metformin plus rosiglitazone arm, and all studies reported no cardiovascular deaths in the metformin monotherapy arms. The results of the 80-week study[127] did not differ from those of the shorter studies.[120, 123, 241] We did not find statistical heterogeneity ($I^2 = 0.0\%$), and removal of any one study from the meta-analysis did not change the inference. The pooled between-group difference for short-term cardiovascular mortality for metformin plus rosiglitazone versus metformin monotherapy was 0.3% (95% CI, -0.2 to 0.9%).

Figure 48. Pooled odds ratio for short-term cardiovascular mortality comparing metformin with a combination of metformin plus rosiglitazone



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus rosiglitazone; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

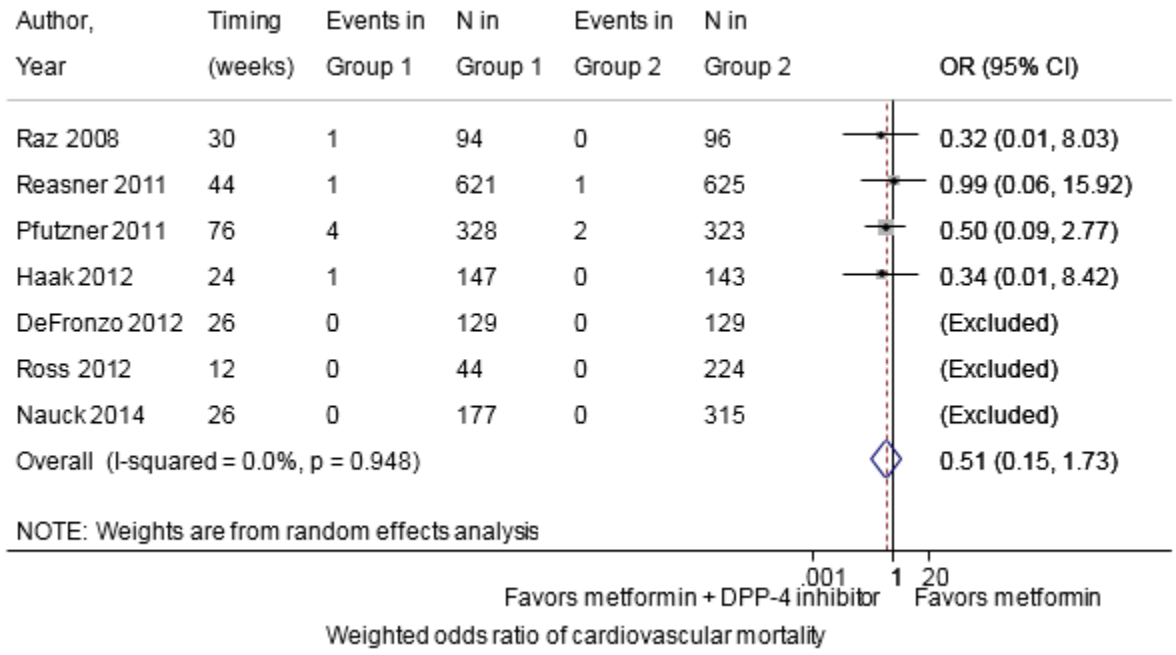
A single 26-week RCT compared metformin monotherapy with metformin plus pioglitazone (15, 30, and 45 mg arms) and reported one sudden cardiac death in the metformin plus pioglitazone 45 mg arm (1/130, 1%). The study did not report on sudden cardiac death for the other arms.[126]

Of note, two of the RCTs had substantial losses to followup (38% to 45% in one study[127] and 12% to 18% in the other[126]). This, along with a lack of reporting on the intention-to-treat population, limits our conclusions. (SOE: Low; Metformin monotherapy favored over combination of metformin plus rosiglitazone for short-term CVD mortality) (SOE: Insufficient for combination of metformin plus pioglitazone)

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Six RCTs comparing metformin with the combination of metformin plus a DPP-4 inhibitor showed a non-significant decreased risk of short-term cardiovascular mortality for the metformin plus DPP-4 inhibitor arms versus metformin, based on 10 deaths across the trials (pooled OR, 0.51; 95% CI, 0.15 to 1.73) (Figure 49). We did not find statistical heterogeneity, and removal of any one study did not change the inference from the meta-analysis.[86, 87, 142, 145, 152, 159] Cardiovascular deaths were not described in the metformin plus saxagliptin arm in Pfutzner 2011, et al, and we assumed that no events occurred in that arm for the meta-analysis.[87] Three of the RCTs included in the meta-analysis also had additional arms with lower dosages and did not report on events in those arms.[86, 87, 126] The pooled between-group difference in short-term cardiovascular mortality was -0.1% (95% CI, -0.4 to 0.3%) for the combination of metformin plus a DPP-4 inhibitor compared with metformin.

Figure 49. Pooled odds ratio for short-term cardiovascular mortality comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a DPP-4 inhibitor; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

An additional longer RCT (104 weeks) reported one cardiovascular death in the metformin plus sitagliptin arm and did not report on cardiovascular deaths in the metformin monotherapy arms.[85] (SOE: Low; Combination of metformin plus DPP-4 inhibitors favored for short-term CVD mortality)

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

One RCT (N=546) compared metformin with the combination of metformin plus dapagliflozin at different doses (2.5, 5.0, and 10.0 mg) and reported two cardiovascular deaths in the metformin plus 2.5-mg dapagliflozin arm at 102 weeks and did not report on deaths in the other arms.[170] (SOE: Insufficient)

Metformin Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

A single 26-week RCT compared metformin with metformin plus dulaglutide at two different doses (0.5 mg and 1.5 mg per week) and reported one fatal stroke in the metformin plus dulaglutide 1.5 mg/week (1/304, 0.3%) arm and no events in the metformin (0/177, 0%) or metformin plus dulaglutide 0.75 mg/week (0/302, 0%) arm.[159] (SOE: Low; Metformin favored for short-term fatal stroke)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a DPP-4 Inhibitor

A single, five-arm, 26-week RCT (N=1,554) compared metformin plus pioglitazone (arms with doses of 15 mg, 30 mg, and 45 mg) with metformin plus alogliptin (12.5-mg and 25-mg arms) and reported on sudden cardiac death.[126] The investigators reported one sudden cardiac death in the metformin plus pioglitazone 45 mg arm (1/129, 0.8%) and did not report on this outcome in the other arms. (SOE: Insufficient)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

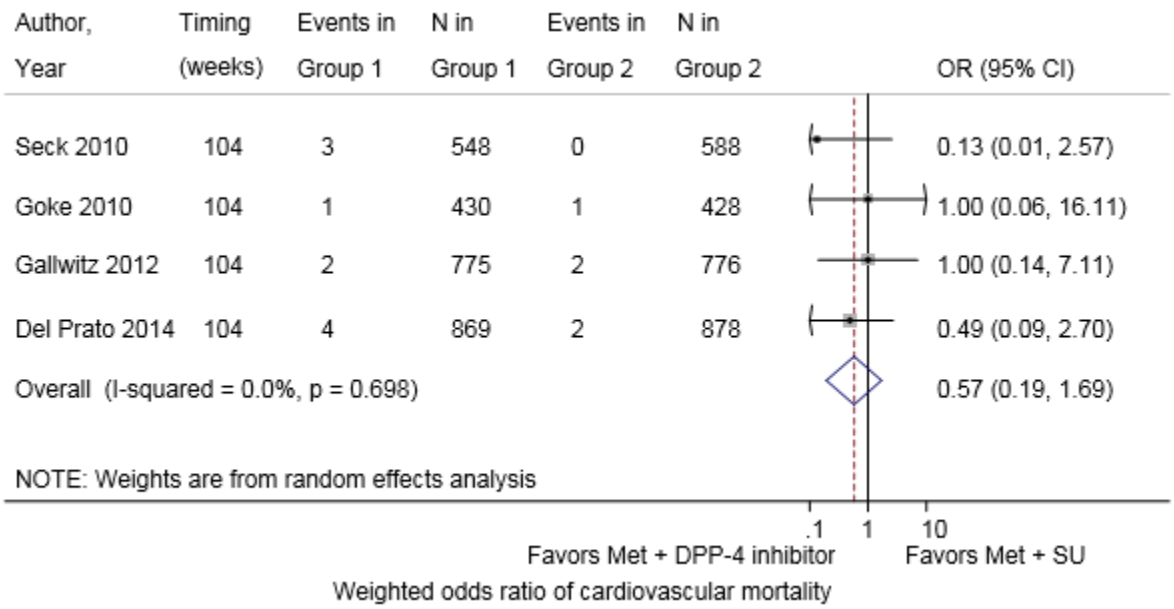
Six RCTs addressed cardiovascular/cerebrovascular mortality for this comparison. Results from four RCTs, each with 104 weeks of followup and low event rates (<1%), suggested lower rates of fatal cardiovascular events for metformin plus a DPP-4 inhibitor versus metformin plus a sulfonylurea (pooled OR, 0.57; 95% CI, 0.19 to 1.69) (Figure 50). We did not find statistical heterogeneity (I^2 = 0.0%).[194-197] Removal of any single study did not change the inference of the meta-analysis. Of note, definitions of cardiovascular mortality varied slightly across the studies included in this meta-analysis (Table 32). Losses to followup were high across these studies. The pooled between-group difference for long-term cardiovascular mortality for metformin plus a DPP-4 inhibitor compared with metformin plus a sulfonylurea was -0.2 (95% CI, -0.5 to 0.1%).

One RCT with 52 weeks of followup conducted among persons (predominantly men) older than 65 years of age reported one fatal myocardial infarction in the metformin plus saxagliptin arm and did not report on this outcome explicitly for the metformin plus sulfonylurea arm.[193]

Two RCTs (N=1,893; durations, 30 weeks and 104 weeks) addressed fatal stroke specifically for this comparison; these reported one event in the metformin plus sulfonylurea arms and did not report on this outcome for the metformin plus DPP-4 inhibitor arms.[190, 195]

A single retrospective cohort study (N=36,230) from the Danish Patient Register reported a significantly lower risk of cardiovascular mortality, with a median of 2.1 years of followup, for metformin plus DPP-4 inhibitor users versus metformin plus sulfonylurea users (adjusted rate ratio, 0.57; 95% CI, 0.4 to 0.8).[227] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored for long-term (2-5 years) CVD mortality; SOE: Insufficient for short-term CVD mortality)

Figure 50. Pooled odds ratio for long-term cardiovascular mortality comparing combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = metformin plus a dipeptidyl peptidase-4 inhibitor; Met = metformin; OR = odds ratio; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Table 32. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor on cardiovascular mortality

Author, Year	Followup (Weeks)	Definition of Fatal Cardiovascular Event	Number of Events / N (%) in the Metformin Plus Sulfonylurea Arm	Number of Events / N (%) in the Metformin Plus DPP-4 Inhibitor Arm	Included in Meta-Analysis
Seck, 2010[196]*	104	Sudden cardiac death, fatal MI	3/548 (0.5%)	0/588 (0)	Yes
Goke, 2010[195]	104	Composite CVD mortality outcome (cardiac failure, MI)	1/430 (0.2%)	1/428 (0.2%)	Yes
Gallwitz, 2012[194]	104	Composite CVD mortality outcome (sudden cardiac death, fatal MI, and fatal stroke)	2/775 (0.3%)	2/776 (0.3%)	Yes
Del Prato, 2014[197]	104	Not specified	4/869 (0.5%)	2/873 (0.2%) (alogliptin 12.5 mg) 2/878 (0.2%) (alogliptin 25 mg)	Yes
Schernthaner, 2015[193]	52	Fatal MI	NR/360	1/360 (0.3%)	No; short-term duration and did not report on events in both arms
Goke, 2010[195]	104	Fatal stroke	1/430 (0.2%)	NR/428	No; did not report on events in both arms
Arechavaleta, 2011[190]	30	Fatal stroke	1/519 (0.2%)	NR/516	No; short-term duration and did not report on events in both arms

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; MI = myocardial infarction
* 104-week followup of Nauck 2007, et al[192]

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Two long-term RCTs (104 weeks of followup) each reported one cardiovascular death in the metformin plus sulfonylurea arm (1/408, 0.2%[199] and 1/482, 0.2%[201]) and no cardiovascular deaths in the metformin plus SGLT-2 inhibitor arms.[199, 201] Therefore, the between-group difference in long-term cardiovascular mortality across trials was 0.2% for the combination of metformin plus a sulfonylurea compared with the combination of metformin plus an SGLT-2 inhibitor. (SOE: Low; Combination of metformin plus a SGLT-2 inhibitor favored for long-term CVD mortality)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

A single retrospective cohort study (N=29,437) from the Danish Patient Register reported a non-significantly lower risk of cardiovascular mortality, with a median of 2.1 years of followup,

for metformin plus GLP-1 receptor agonist users versus metformin plus sulfonylurea users (adjusted rate ratio, 0.89; 95% CI, 0.47 to 1.68).[227] (Not graded)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a Basal Insulin

A single retrospective cohort study (N=29,437) from the Danish Patient Register reported a significantly increased risk of cardiovascular mortality, with a median of 2.1 years of followup, for metformin plus basal insulin users versus metformin plus sulfonylurea users (adjusted rate ratio, 1.57; 95% CI, 1.23 to 2.01).[227] (Not graded)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a Premixed Insulin

A single 16-week, open-label RCT (N=341) randomized participants with poorly controlled diabetes on metformin alone to the addition of glibenclamide or twice daily insulin aspart 70/30 and reported no deaths in the metformin plus glibenclamide arm and one fatal myocardial infarction in the metformin plus premixed insulin arm.[208] (SOE: Low; Combination of metformin plus sulfonylurea favored for short-term CVD mortality)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

A single 26-week, open-label RCT (N=665) randomized participants with poorly controlled diabetes on metformin alone to the addition of oral sitagliptin (100 mg) or one of two doses of daily subcutaneous injections of liraglutide (1.2 mg or 1.8 mg) and reported one fatal cardiac arrest in the metformin plus sitagliptin arm (1/219, 0.5%) and none in the metformin plus liraglutide arms (liraglutide 1.2 mg: 0/221, 0% and liraglutide 1.8 mg: 0/218, 0%).[210]

A single 26-week RCT (N=921) reported on fatal stroke for metformin plus sitagliptin versus metformin plus dulaglutide at two doses (0.75 mg/week and 1.5 mg/week). The investigators reported one fatal stroke in the metformin plus dulaglutide 1.5-mg/week arm (1/304, 0.3%) and no events in the other arms (dulaglutide 0.75 mg: 0/302, 0% and sitagliptin: 0/315, 0%).[159] (SOE: Insufficient)

Combination of Metformin Plus a Basal Insulin Versus a Combination of Metformin Plus a Premixed Insulin

A single 32-week, open-label, cross-over study (N=597) randomized participants to metformin plus insulin glargine or metformin plus insulin lispro 75/25 twice daily and reported one fatal myocardial infarction in the metformin plus insulin lispro 75/25 arm and no events in the metformin plus glargine arm.[224] (SOE: Insufficient)

Strength of Evidence for Cardiovascular Mortality

Although we identified one comparison for which there was moderate strength of evidence on long-term cardiovascular mortality, evidence was generally of low strength or insufficient for cardiovascular mortality (see Key Points, Table 33, Table 34, and Table 35). Most of the evidence was on short-term cardiovascular mortality, and none of the RCTs were designed to evaluate cardiovascular mortality. We identified observational studies which strengthened the evidence for a few comparisons (metformin versus sulfonylurea and metformin plus a sulfonylurea versus metformin plus DPP-4 inhibitors). Almost all of the evidence on

cardiovascular mortality was of medium or high risk of bias. When data were available from more than one study for a given comparison, the evidence tended to be consistent. However, we only identified a single study for many comparisons making consistency indeterminate. Sample size and low event rates in the RCTs limited the power and precision of the evidence on cardiovascular mortality, and the small number of studies limited our ability to assess publication bias. We identified one unpublished study (an extension of an included study with 156 weeks of followup) which addressed several comparisons of interest. This study had few fatal cardiovascular or cerebrovascular events (none in the metformin arm or metformin plus GLP-1 receptor agonist arm; one fatal MI in the metformin plus sitagliptin arm; and one fatal cerebrovascular accident in the metformin plus sulfonylurea arm). This study's results were slightly contrary to our findings on metformin plus a sulfonylurea versus metformin plus a DPP-4 inhibitor. While we did not identify any published RCTs comparing cardiovascular mortality for metformin versus metformin plus a sulfonylurea, the unpublished RCT suggested similar long-term fatal cardiovascular mortality for metformin and metformin plus sulfonylurea, but possibly an increased risk of fatal cerebrovascular accident in the metformin plus sulfonylurea arm versus metformin. We also did not identify long-term RCTs of metformin plus a DPP-4 inhibitor versus metformin plus a GLP-1 receptor agonist; in this long-term unpublished study, metformin plus sitagliptin was favored for this comparison.

Table 33. Strength of evidence domains for monotherapy comparisons in terms of cardiovascular mortality among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. pioglitazone	RCTs: 2 (120)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. rosiglitazone	RCT: 1 (2940)	High	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. SU (longer duration studies)	RCTs: 2 (4664) Observational: 3 (115,105)	Medium Medium	Consistent Consistent	Direct Direct	Imprecise Precise	Undetected Undetected	Moderate	Metformin favored; RR 1.6 to 2.0 and between group differences 0.1% to 2.9% from RCTs for SU vs. metformin
Metformin vs. DPP-4 inhibitors	RCTs: 3 (3,188)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	DPP-4 inhibitors favored for short-term mortality
Rosiglitazone vs. SU (longer-duration studies)	RCT: 1 (2,987)	High	Unknown	Direct	Imprecise	Undetected	Low	Rosiglitazone favored
SU vs. DPP-4 inhibitors (shorter duration studies)	RCT: 2 (653)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine Events not reported for all arms

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95% confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Table 34. Strength of evidence domains for metformin versus metformin-based combination comparisons in terms of cardiovascular mortality among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + rosiglitazone	RCTs: 5 (2,167)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin favored for short-term mortality
Metformin vs. metformin + pioglitazone	RCT: 1 (1,554)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. metformin+DPP-4 inhibitor	RCTs: 7 (6,673)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin + DPP-4 inhibitors favored for short-term mortality
Metformin vs. metformin + SGLT-2 inhibitor	RCT: 1 (546)	Low	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine Events not reported on in three arms
Metformin vs. metformin + GLP-1 receptor agonist	RCT: 1 (1098)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin favored for short-term fatal stroke

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; RD = risk difference; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95% confidence intervals) and pooled risk differences (95% confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Table 35. Strength of evidence domains for metformin-based combination comparisons in terms of cardiovascular mortality among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + pioglitazone vs. metformin + DPP-4 inhibitor	RCT: 1 (1554)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine Events not reported on in four arms
Metformin + SU vs. metformin + DPP-4 inhibitors (104 weeks followup)	RCTs: 4 (6184) Observational: 1 (36,620)	Medium Medium	Inconsistent Unknown	Direct Direct	Imprecise Precise	Undetected N/A	Low	Metformin + DPP-4 inhibitors favored for long-term CVD mortality
Metformin + SU vs. metformin + DPP-4 inhibitors (shorter duration studies)	RCTs: 2 (1755)	Medium	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine Events not reported on in all arms
Metformin + SU vs. metformin + SGLT-2 inhibitor (longer duration studies)	RCT: 2 (2266)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin + SGLT-2 inhibitors favored
Metformin + SU vs. metformin + premixed insulin	RCT: 1 (341)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin + SU favored for short-term CVD mortality
Metformin + DPP-inhibitor vs. metformin + GLP-1 receptor agonist	RCTs: 2 (1,763)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + basal insulin vs. metformin + premixed insulin	RCT: 1 (597)	Medium	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine

CVD = cardiovascular; DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95% confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Cardiovascular and Cerebrovascular Morbidity

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Randomized Controlled Trials

Two RCTs compared metformin with rosiglitazone and reported on different cardiovascular morbidity outcomes.[50, 59] In ADOPT, at 4 years, there was a small increased risk of non-fatal MI for the rosiglitazone vs. metformin arm (between-group difference of 0.3 absolute percentage points) and an increased risk of peripheral vascular disease (between-group difference of 0.6 absolute percentage points). There was also a small increased risk of stroke in the metformin vs. rosiglitazone arm (between-group difference of 0.2 absolute percentage points).[50] Total CVD event rates were higher (by 0.7%) in the rosiglitazone (77/1456, 5.3%) vs. metformin (67/1454, 4.6%) arm. The completeness of ascertainment of CVD morbidity was unclear, and losses to followup were 37% and 38% for the rosiglitazone and metformin arms, respectively.[50] Event rates in the small 32-week study were the same in both arms (Table 36).[59]

Table 36. Randomized controlled trials comparing metformin with rosiglitazone on cardiovascular morbidity

Author, Year	Enrolled N	Followup	Outcome	Number of Events / N (%) for Metformin Vs. Rosiglitazone
Kahn*, 2006[50]	4360	4 years (median)	Non-fatal myocardial infarction	21/1454 (1.4) vs. 25/1456 (1.7)
			Stroke	19/1454 (1.3) vs. 16/1456 (1.1)
			Peripheral vascular disease	27/1454 (1.9) vs. 36/1456 (2.5)
Rosenstock, 2006[59]	468	32 weeks	Not defined ischemic heart disease	2/154 (1) vs. 1/159 (1)

* ADOPT Study

Three small RCTs, each shorter than a year, compared metformin with pioglitazone and reported very few events.[63, 70, 71] We did not perform a meta-analysis given the absence of events in two of the three studies and lack of reporting in the third (Table 37).

Table 37. Randomized controlled trials comparing metformin with pioglitazone on cardiovascular morbidity

Author, Year	Enrolled N	Followup	Outcome	Number of Events / N (%) for Metformin Vs. Pioglitazone
Erem, 2014[70]	57	48 weeks	Nonfatal MI	0/19 (0) vs. 0/9 (0)
Lawrence, 2004[63]	60	24 weeks	Nonfatal CVD morbidity/MI	0/20 (0) vs. 0/20 (0)
Genovese, 2013[71]	58	16 weeks	Discontinuation due to myocardial ischemia	1/29 (3.4) vs. NR/29

CVD = cardiovascular disease; MI = myocardial infarction; NR = not reported

Observational Studies

Three retrospective cohort studies[233, 243, 244] compared metformin with rosiglitazone and reported mixed results (Table 38). One study reported no increased risk of ischemic heart disease for rosiglitazone versus metformin,[233] and the other two studies suggested an increased risk of cardiovascular morbidity for rosiglitazone versus metformin.[243, 244]

(SOE: Low; Metformin favored for long-term (follow up at least 2 years) CVD morbidity)

Table 38. Retrospective cohort studies comparing metformin with rosiglitazone on cardiovascular morbidity

Author, Year	Population (N)	Followup	Outcome	Adjusted HR (95% CI)
Pantalone, 2009[233]	Cleveland Clinic electronic health record system (11,515)	8 years	Ischemic heart disease	0.96 (0.76 to 1.21) Reference = metformin
Hsiao, 2009[243]	Taiwan National Health Insurance – newly-diagnosed diabetes (48,537)	6 years	Myocardial infarction Angina pectoris Transient ischemic attack Stroke	2.09 (1.36 to 3.24) 1.79 (1.39 to 2.30) 2.57 (1.33 to 4.96) 1.61 (0.72 to 3.62) Reference = metformin
Brownstein, 2010[244]	United States (34,252)	7 years	Hospitalization for acute MI	3.0 (2.4 to 3.7) Reference = metformin

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction

Two of the retrospective cohort studies compared metformin with pioglitazone[233, 243] and found no significant difference in cardiovascular disease risk between groups (Table 39). Of note, participants in the Taiwan National Health Insurance database study prescribed pioglitazone were more likely to have a history of cardiovascular disease than those prescribed metformin.[243] (SOE: Moderate; Neither metformin nor pioglitazone favored)

Table 39. Retrospective cohort studies comparing metformin with pioglitazone on cardiovascular morbidity

Author, Year	Population (N)	Followup	Outcome	Adjusted HR (95% CI)
Pantalone, 2009[233]	Cleveland Clinic electronic health record system (11944)	8 years	Ischemic heart disease	1.11 (0.91 to 1.34) Reference = metformin
Hsiao, 2009[243]	Taiwan National Health Insurance – newly-diagnosed diabetes (46,939)	6 years	Myocardial infarction Angina pectoris	1.0 (0.26 to 3.89) 1.15 (0.6 to 2.21) Reference = metformin

CI = confidence interval; HR = hazard ratio

Metformin Versus Sulfonylureas

Randomized Controlled Trials

Three RCTs[50, 134, 231] compared metformin with sulfonylureas and reported on cardiovascular morbidity (Table 40). Two of these RCTs had long-term followup. In ADOPT, the risk of nonfatal myocardial infarction and stroke were higher in the metformin versus sulfonylurea arm (between-group differences of 0.4% and 0.1% for nonfatal myocardial infarction and stroke, respectively). Notably, losses to followup and duration of followup were differential across these arms with higher losses to followup (44% versus 38%) and shorter median followup (3.3 versus 4.0 years) for sulfonylurea versus metformin.[50] Cardiovascular event rates were higher for sulfonylurea versus metformin in the other long-term RCT, which was conducted in a predominantly-male, Chinese population with an established diagnosis of coronary heart

disease.[231] Losses to followup were the same (21%) for both arms of this trial.[231] The third RCT was small and short (6 months) and found higher rates of undefined cardiovascular morbidity in the sulfonylurea than metformin arm.[134]

Table 40. Randomized controlled trials comparing metformin with sulfonylureas on cardiovascular morbidity

Author, Year	Followup	Outcome	Number of Events / N (%) for Metformin Vs. Sulfonylurea
Kahn, 2006[50]	4 years (median)	Non-fatal MI	21/1454 (1.4) vs. 15/1441 (1.0)
		Stroke	19/1454 (1.3) vs. 17/1441 (1.2)
		Peripheral vascular disease	27/1454 (1.9) vs. 31/1441 (2.2)
Hong, 2013[231]	2.8 years	Non-fatal MI confirmed by medical records	5/156 (3.2) vs. 6/148 (4.1)
		Non-fatal stroke confirmed by medical records	10/156 (6.4) vs. 15/148 (10)
		Arterial revascularization by PTCA or by coronary artery bypass graft confirmed by medical records	21/156 (14) vs. 25/148 (17)
		CVD morbidity composite outcome*	39/156 (25) vs. 52/148 (35)
		New critical cardiac arrhythmia confirmed by medical record	30/156 (19) vs. 27/148 (18)
		New or worsening angina confirmed by medical record	77/156 (49) vs. 71/148 (48)
		New peripheral vascular disease events confirmed by medical record	1/156 (0.6) vs. 6/148 (4.1)
Hermann, 1994[134]	6 months	Unclear – CVD morbidity/CHD	2/25 (5) vs. 3/21 (9)

CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty

* Including nonfatal myocardial infarction, nonfatal stroke, or arterial revascularization by PTCA or by coronary artery bypass graft, death from a cardiovascular cause, and death from any cause, obtained and confirmed by medical record.

Observational Studies

Five retrospective cohort studies[229, 233, 238, 245, 246] and one case-control study[226] reported on cardiovascular morbidity for metformin and sulfonylurea use (Table 41 and Table 42). All but one study[233] reported a significantly increased risk of incident cardiovascular morbidity among sulfonylurea versus metformin users.[226, 229, 233, 238, 245, 246] This risk extended to populations without a history of cardiovascular disease at baseline.[229, 238]

(SOE: Low; Metformin favored for long-term CVD morbidity)

Table 41. Retrospective cohort studies comparing metformin with sulfonylureas on cardiovascular morbidity

Author, Year	Population (N)	Followup	Outcome	Adjusted HR (95% CI)
Pantalone, 2009[233]	Cleveland Clinic EHR system (17863)	8 years	Incident ischemic heart disease by ICD-9 code	0.94 (0.85 to 1.05) Reference = sulfonylurea
Hung, 2013[245]	Taiwan National Health Insurance Research Database (N=925)	Median 3.1 to 3.8 years	Composite cardiovascular outcome based on ICD-9 codes	0.31 (0.24 to 0.4) Reference = sulfonylurea
Roumie, 2012[246]	Veterans Administration database linked to Medicare files (N= 253,690)	0.61 to 0.78 years	Hospitalization for acute MI, stroke, or death	1.21 (1.13 to 1.29)* Reference = metformin
			Acute MI and stroke	1.15 (1.06 to 1.25)* Reference = metformin
Schramm, 2011[229]	Danish Patient Register (N=107,806)	Median 3.3 years	Composite of MI, stroke and cardiovascular death based on ICD-10 codes	Prior MI 1.29 (1.09 to 1.52)† 1.46 (1.2 to 1.78)‡ 1.29 (1.12 to 1.49)§ No prior MI 1.12 (1.04 to 1.21)† 1.17 (1.07 to 1.28)‡ 1.21 (1.14 to 1.29)§ Reference = metformin
Corrao, 2011[238]	Health Service Databases Lombardy (N=70,437)	Mean 4.8 to 5.1 years	Composite of death from any cause or first hospitalization for MI, cerebrovascular disease, or coronary artery bypass graft based on ICD-9	1.15 (1.08 to 1.21) Reference = metformin

CI = confidence interval; EHR = electronic health record; HR = hazard ratio; ICD = International Classification of Diseases; MI = myocardial infarction

*33% to 39% data missing on hemoglobin A1c (covariate in model)

† glibenclamide

‡ glipizide

§ glimepiride

Table 42. Nested case-control study comparing metformin with sulfonylureas on hospitalization for incidence of myocardial infarction

Authour, Year	Population Followup	Cases	Controls	Adjusted OR (95% CI)
Horsdal, 2011[226]	Danish National Patient Registry Median 6 months	First-time hospitalization for non-fatal MI (N=10,616)	Age- and gender-matched patients with diabetes and no history of MI (N=90,697)	0.86 (0.78 to 0.95) Reference = sulfonylurea

CI = confidence interval; MI = myocardial infarction; OR = odds ratio

Metformin Versus DPP-4 Inhibitors

Two RCTs compared metformin with DPP-4 inhibitor monotherapy and reported on cardiovascular morbidity. One small, 26-week RCT of low quality reported one nonfatal myocardial infarction in the alogliptin arm (1/112, 1%) and did not report on events in the metformin arms (n=109 and n=111 for the 1000-mg and 2000-mg arms, respectively). This study noted that it evaluated nonfatal stroke but did not report these outcomes.[84] This study did not use an intention-to-treat approach for cardiovascular morbidity and had greater than 17 percent

losses to followup in both arms.[84] A second larger and longer (76 weeks) RCT of higher quality reported that 2.1 percent of participants in the metformin arm (n=328) experienced an acute cardiovascular adverse event (otherwise unspecified) and did not report on this outcome in the saxagliptin arm (n=335).[87]

A single retrospective cohort study from the Danish National Patient Registry (N=84,756) reported a non-significant increase in cardiovascular risk (composite outcome: all-cause mortality, acute myocardial infarction, and stroke) for sitagliptin versus metformin over mean followup of 0.9 to 1.8 years (adjusted RR, 1.22; 95% CI, 0.92 to 1.61).[228] (SOE: Insufficient)

Metformin Versus SGLT-2 Inhibitors

A single 12-week RCT reported one episode of Prinzmetal angina in the metformin arm (1/80, 1.3%) and did not report on events in the empagliflozin 10 mg (n=81) or empagliflozin 25 mg (n=82) arms.[239] This study did not use an intention-to-treat approach and did not report on withdrawals.[239] (SOE: Insufficient)

Thiazolidinediones Versus Sulfonylureas

Two RCTs[50, 217] and two retrospective cohort studies[243, 244] compared the effects of sulfonylureas and rosiglitazone on cardiovascular morbidity (Table 43). In the long-term RCT, ADOPT, CVD morbidity was higher in the rosiglitazone versus sulfonylurea arm (between-group difference of 0.7% for in nonfatal MI and 0.1% for stroke); losses to followup (44% versus 37%) were higher in the sulfonylurea arm while followup duration was shorter.[50] Results of the shorter RCT were consistent with ADOPT.[217] CVD morbidity was non-statistically significantly higher for rosiglitazone versus a sulfonylurea in two of three observational studies.[243, 244]

A single short-term RCT[95] reported a 0.2% increase in coronary heart disease morbidity for glyburide versus pioglitazone at 56 weeks (Table 44). Long-term cohort studies compared the effects of sulfonylureas and pioglitazone and reported mixed findings.[233, 243] (SOE: Low; Sulfonylureas favored over rosiglitazone) (SOE: Low; Sulfonylureas favored over rosiglitazone for long-term CVD morbidity; Low; Pioglitazone favored for short-term CVD morbidity)

Table 43. Studies comparing rosiglitazone with sulfonylureas on cardiovascular morbidity

Author, Year Study Design	Population (N)	Followup	Outcome	Results
Kahn, 2006[50] RCT	ADOPT Study (4360)	4.0 years for rosiglitazone 3.3 years for SU (median)	Nonfatal MI Stroke Peripheral vascular disease	Rosiglitazone: 1.7%; SU: 1.0% Rosiglitazone: 1.3%; SU: 1.2% Rosiglitazone: 2.5%; SU: 2.2%
St John Sutton, 2002[217] RCT	N=351	52 weeks	Cardiac-related adverse events	Rosiglitazone: 15.4%; SU: 12.1%
Pantalone, 2009[233] Retrospective cohort	Cleveland Clinic electronic health record system (8506)	8 years	Incident ischemic heart disease by ICD-9 code	Adjusted HR 0.90; 95% CI, 0.71 to 1.14 Reference = sulfonylurea
Hsiao, 2009[243] Retrospective cohort	Taiwan National Health Insurance – newly-diagnosed diabetes (99744)	6 years	MI Stroke Transient ischemic attack Angina pectoris	Adjusted HR 1.49; 95% CI, 0.99 to 2.24 Adjusted HR 1.45; 95% CI, 0.69 to 3.05 Adjusted HR 1.90; 95% CI,1.02 to 3.57 Adjusted HR 1.46; 95% CI, 1.15 to 1.85 Reference = sulfonylurea
Brownstein, 2010[244] Retrospective cohort	Research Patient Data Registry (34,252)	7 years	Hospitalization for MI	Adjusted RR, 1.3; 95% CI, 1.0 to 1.6 Reference = sulfonylurea

ADOPT = A Diabetes Outcome Progression Trial; CI = confidence interval; HR = hazard ratio; ICD = International Classification of Diseases; MI = myocardial infarction; RCT = randomized controlled trial; RR = rate ratio

Table 44. Studies comparing pioglitazone with sulfonylureas on cardiovascular morbidity

Author, Year Study Design	Population (N)	Followup	Outcome	Results
Jain, 2006[95] RCT	N=502	56 weeks	CHD, MI and chest pain	Pioglitazone: 1%; glyburide: 3%
Pantalone, 2009[233] Retrospective cohort	Cleveland Clinic electronic health record system (8935)	8 years	Incident ischemic heart disease by ICD-9 code	Adjusted HR 1.04; 95% CI, 0.86 to 1.26 Reference = sulfonylurea
Hsiao, 2009[243] Retrospective cohort	Taiwan National Health Insurance – newly-diagnosed diabetes (98146)	6 years	MI Stroke Transient ischemic attack Angina pectoris	Adjusted HR 0.72; 95% CI, 0.19 to 2.77 Adjusted HR 0.59; 95% CI, 0.06 to 6.03 Adjusted HR 1.28; 95% CI, 0.34 to 4.86 Adjusted HR 0.91; 95% CI, 0.47 to 1.74 Reference=sulfonylurea

CHD = coronary heart disease; CI = confidence interval; HR = hazard ratio; ICD = International Classification of Diseases; MI = myocardial infarction; RCT = randomized controlled trial

Sulfonylureas Versus DPP-4 Inhibitors

Two RCTs (each 52 to 58 weeks duration) compared the effects of sulfonylureas with DPP-4 inhibitors on short-term cardiovascular morbidity.[106, 107] One study reported one nonfatal myocardial infarction in one participant in the sulfonylurea arm (1/76, 1.3%) and no events in the linagliptin arm (0/151, 0.0%); the between-group risk difference was 1.3% for sulfonylurea versus linagliptin.[106] The other study reported 11 vascular events in the sulfonylurea arm (11/212, 5.2%) and eight events in the sitagliptin arm (8/210, 3.8%); the between-group risk difference was 1.4% for the sulfonylurea versus sitagliptin arm.[107] The dose of glimepiride was low in one study (4 mg).[106] The study by Arjona Ferreira et al did not use an intention-to-treat approach and had greater than 20 percent losses to followup across arms.[107] (SOE: Low; DPP-4 inhibitors favored for short-term cardiovascular morbidity)

Sulfonylureas Versus GLP-1 Receptor Agonists

Two RCTs compared the effects of sulfonylurea with liraglutide on cardiovascular morbidity and reported slightly higher rates of cardiovascular events in the sulfonylurea arms compared with the liraglutide arms. In the longer study (104 weeks), 14 of 248 (6%) participants experienced a cardiac disorder in the sulfonylurea arm, and eight of 251 (3%) participants and 11 of 246 (5%) participants experienced a cardiac disorder in the liraglutide 1.2 mg and 1.8 mg arms, respectively (between-group differences of 1 to 3% for sulfonylurea versus liraglutide).[113] The other RCT (N=200) was 52 weeks and reported higher rates of vascular (7.6% versus 6.3%; between-group difference, 1.3%) and cardiac (10.6% versus 6.3%; between-group difference, 4.3%) disorders in the sulfonylurea arm compared with the liraglutide arm.[110] Of note, Kaku et al. used low doses of glibenclamide (1.25 to 2.5 mg/day) and liraglutide (0.9 mg/day).[110] (SOE: Low; GLP-1 receptor agonists favored)

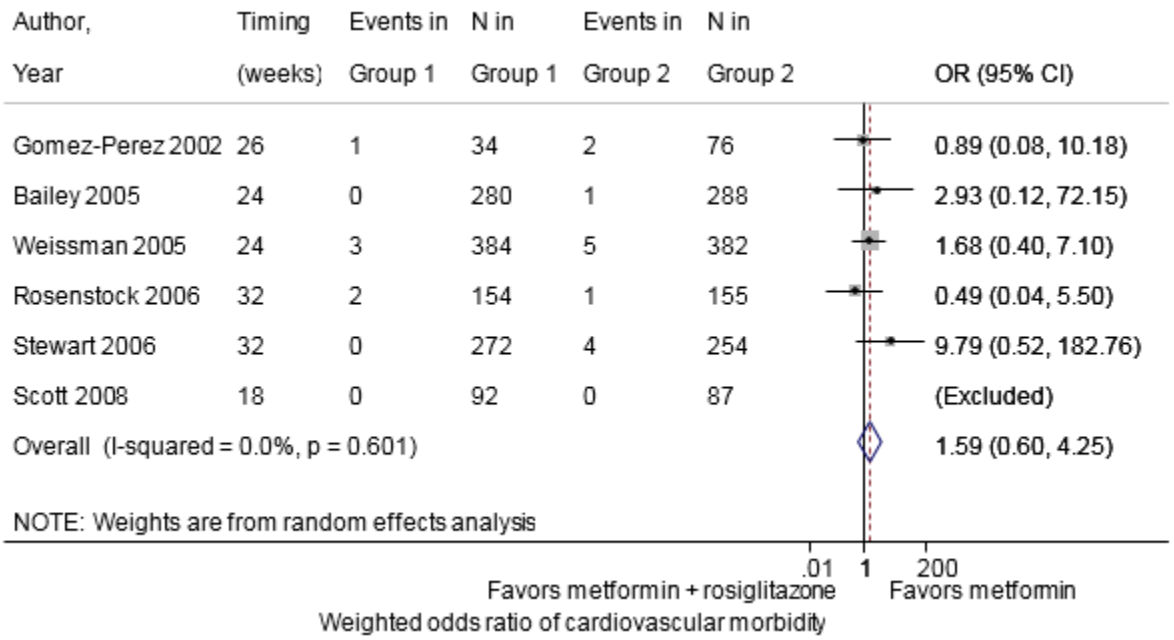
Metformin Versus a Metformin-Based Combination Comparison

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Six short-term (18 to 32 weeks) RCTs found a non-significant increase in cardiovascular morbidity for metformin plus rosiglitazone versus metformin (pooled OR, 1.59; 95% CI, 0.60 to 4.25) (Figure 51).[59, 118-121, 247] Removal of any one study did not change the inference of the meta-analysis. The pooled risk difference for short-term CVD morbidity for metformin plus rosiglitazone versus metformin was 0.4% (95% CI, -0.2 to 1.1%).

Another longer RCT (80 weeks of followup) reported four ischemic events (4/344, 1.7%) and five cerebrovascular events (5/344, 1.5%) in the metformin plus rosiglitazone arm compared with four ischemic events (4/334, 1.2%) and three cerebrovascular events (3/334, 0.9%) in the metformin arm.[127] Of note, the text of article contradicts results in the table (reported here); the text reports five ischemic events in the metformin arm.[127] (SOE: Low; Metformin favored over combination of metformin plus rosiglitazone for short-term cardiovascular morbidity)

Figure 51. Pooled odds ratio of cardiovascular morbidity comparing metformin with a combination of metformin plus rosiglitazone



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus rosiglitazone; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

A single 26-week RCT compared metformin to metformin plus pioglitazone (dosed at 15, 30, and 45 mg in separate arms) and reported one nonfatal stroke in the metformin arm (1/129) and did not report on this outcome for the metformin plus pioglitazone arms (n=388).[126] (SOE: Insufficient)

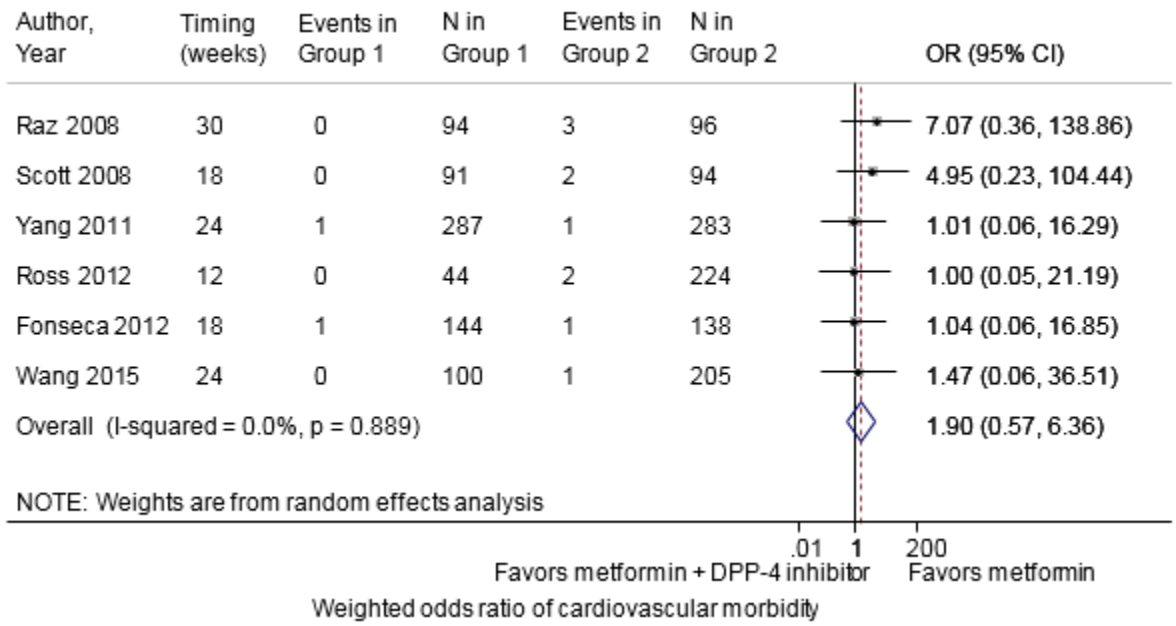
Metformin Versus a Combination of Metformin Plus a Sulfonylurea

One 6-month RCT,[134] which was a good although older study, reported rates of 5% and 14% for unspecified cardiovascular events in the metformin versus combination metformin plus sulfonylurea arm, respectively.[134] (SOE: Low; Metformin favored for short-term CVD morbidity)

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Six short RCTs compared the combination of metformin plus a DPP-4 inhibitor with metformin monotherapy and found no significant difference in short-term cardiovascular morbidity based on 11 events across studies (pooled OR, 1.90; 95% CI, 0.57 to 6.36) (Figure 52).[118, 142, 146, 147, 152, 160] We did not find statistical evidence of heterogeneity, and removal of any one study did not change the inference of this meta-analysis. The pooled risk difference for short-term cardiovascular morbidity for metformin plus a DPP-4 inhibitor versus metformin was 0.3% (95% CI, -0.4% to 1.1%).

Figure 52. Pooled odds ratio of short-term cardiovascular morbidity comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

We did not include one RCT (N=651) in the meta-analysis because of its longer duration (76 weeks). The investigators reported a rate of 2.1% for acute cardiovascular adverse events in the metformin arm, 0.3% in the metformin plus saxagliptin 5 mg arm, and did not report this rate in the metformin plus saxagliptin 10 mg arm.[87]

We did not include three additional RCTs in the meta-analysis because of a lack of reporting of events in at least one arm precluding estimation of an OR (Table 45). Cardiovascular

morbidity was slightly higher in the combination therapy arms based on the limited results reported.[84, 151, 164]

Table 45. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on cardiovascular morbidity

Author, Year	Followup (Weeks)	Outcome	Number of Events / N (%) for Metformin Vs. Metformin + DPP-4 Inhibitor
Raz, 2008[142]	30	Acute MI	Results presented in Figure 52
Yang, 2011[146]	24	Acute myocardial ischemia or MI	Results presented in Figure 52
Wang, 2015[160]	24	Nonfatal MI	Results presented in Figure 52
Scott, 2008[118]	18	Acute CV event	Results presented in Figure 52
Fonseca, 2012[147]	18	Acute CV events (myocardial ischemia or MI	Results presented in Figure 52
Ross, 2012[152]	12	Acute MI	Results presented in Figure 52
Pfutzner, 2011[87]	76	Acute CV events	NR/328 (2.1) Metformin + saxagliptin 5 mg: NR/320 (0.3) Metformin + saxagliptin 10 mg: NR/323 (NR)
Haak, 2013[164]	52	Nonfatal MI	1/170 (0.6) Metformin 2000 mg + linagliptin: NR /171 Metformin 1000 mg + linagliptin: 3/225 (1.3)
		Unstable angina	NR/170 (0.6) Metformin 2000 mg + linagliptin: 2/171 (1.2) Metformin 1000 mg + linagliptin: 2/225 (0.9)
White, 2014[151]	12	Nonfatal MI	NR/86 1/74 (1.4)
Pratley*, 2014[84]	26	Nonfatal MI	Metformin 2000 mg: NR/111 Metformin 1000 mg: NR/109 Metformin 2000 mg + alogliptin: NR/114 Metformin 1000 mg + alogliptin: NR/106

CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; mg = milligrams; MI = myocardial infarction; NR = not reported
* included in table even though did not report on outcome for any of the arms because study did provide results for alogliptin monotherapy arm implying that there were likely no nonfatal myocardial infarctions in the other arms

Four short-term RCTs comparing metformin with metformin plus a DPP-4 inhibitor reported on nonfatal stroke but did not report on events in all arms (Table 46).[84, 126, 160, 164] Nonfatal strokes were uncommon and appeared more common in the metformin monotherapy arms based on limited reporting of results on this outcome. (SOE: Insufficient for short-term cardiovascular morbidity)

Table 46. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on nonfatal stroke

Author, Year	Followup (Weeks)	Number of Events / N (%) for Metformin Vs. Metformin + DPP-4 Inhibitor
Haak, 2013[164]	52	1/170 (0.6) Metformin 2000 mg + linagliptin: NR/171 Metformin 1000 mg + linagliptin: 1/225 (0.4)
DeFronzo, 2012[126]	26	1/129 (0.8) Metformin + alogliptin 12.5 mg: NR/128 Metformin + alogliptin 25 mg: NR/129
Pratley, 2014[84]	26	Metformin 2000 mg: NR/111 Metformin 1000 mg: NR/109 Metformin 2000 mg + alogliptin: NR/114 Metformin 1000 mg + alogliptin: NR/106
Wang, 2015[160]	24	1/100 (1) Metformin + linagliptin 5 mg: 0/205 (0)

DPP-4 = dipeptidyl peptidase-4; mg = milligrams; NR = not reported

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

A single 24-week RCT (N=182) compared the effects of metformin with metformin plus dapagliflozin on cardiovascular morbidity. This study reported that two participants (2/91, 2.2%) developed angina pectoris in the metformin plus dapagliflozin arm and that there were no events in the metformin arm (0%).[169] The investigators also reported one transient ischemic attack in the metformin plus dapagliflozin arm (1/91, 1.1%) and did not report on this outcome in the metformin arm.[169] (SOE: Low; Metformin favored for short-term cardiovascular morbidity)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Two short-term RCTs compared metformin plus pioglitazone with metformin plus a sulfonylurea and reported mixed results on cardiovascular morbidity.[183, 185] One trial (N=288) with submaximally-dosed pioglitazone (30 mg/day) reported three events (coronary heart disease, carotid artery stenosis, and peripheral artery disease) among 142 participants (2%) at 24 weeks in the metformin plus sulfonylurea arm and did not report on events in the metformin plus pioglitazone arm.[185] The other RCT (N=250) reported one acute myocardial infarction at 24 weeks in the metformin plus pioglitazone arm (1/103, 1%) versus no events in the metformin plus sulfonylurea arm (0%).[183]

A single retrospective cohort study from a Veterans Affairs population with Medicare (N=80,936) compared the combination of metformin plus a thiazolidinedione with metformin plus a sulfonylurea and found a non-significant increase in risk of stroke or myocardial infarction (composite outcome) for sulfonylurea-based versus thiazolidinedione-based therapy: adjusted HR, 1.15 (95% CI, 0.8 to 1.66; p=0.46); minimum followup was 12 months, but mean duration of followup was not reported.[242] (SOE: Insufficient)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Two RCTs compared metformin plus pioglitazone with metformin plus a DPP-4 inhibitor at 26 weeks and reported on cerebrovascular events.[126, 188] One reported a cerebrovascular accident in each arm (1/165, 1% in the metformin plus pioglitazone arm and 1/166, 1% in the metformin plus sitagliptin arm),[188] and the other did not report on cerebrovascular events in the combination therapy arms (reported events for monotherapy as discussed above).[126] Bergenstal 2010 et al., also reported three cardiovascular events (unstable angina, n=1; coronary artery occlusion, n=2) in the metformin plus pioglitazone group and no events in the metformin plus sitagliptin (0/166, 0%) group.[188] This RCT did not use an intention-to-treat approach and had differential and large losses to followup (13% in the metformin plus DPP-4 inhibitor arm and 21% in the metformin plus pioglitazone arm).[188] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored over metformin plus pioglitazone for short-term cardiovascular morbidity)

Two RCTs compared metformin plus rosiglitazone with metformin plus sitagliptin (duration 16 to 18 weeks) and reported on cardiovascular and cerebrovascular morbidity.[118, 186] The trial evaluating cardiovascular events reported none in the metformin plus rosiglitazone arm (0/87, 0%) and two coronary artery disease events in the metformin plus sitagliptin arm (2/94, 2.1%).[118] The other trial (N=169) reported a transient ischemic attack in each arm.[186] (SOE: Low;

combination of metformin plus rosiglitazone favored over metformin plus DPP-4 inhibitor for short-term cardiovascular morbidity)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

One RCT (N=325) compared metformin plus pioglitazone with metformin plus exenatide at 26 weeks and reported one cerebrovascular accident (1/165, 1%) and three cardiac events (unstable angina and coronary artery occlusions; 3/165, 2%) in the metformin plus pioglitazone arms and no events in the metformin plus exenatide arm (0/160, 0%).[188] (SOE: Low; Combination of metformin plus a GLP-1 receptor agonist favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Four RCTs reported on long-term cardiovascular morbidity for the comparison of metformin plus sulfonylurea with metformin plus a DPP-4 inhibitor (Tables 47 and 48).[192, 194-197]

Three of these 104-week studies provided results on non-fatal myocardial infarction and showed a non-significant decrease in fatal myocardial infarction for the combination of metformin plus a DPP-4 inhibitor versus metformin plus a sulfonylurea (pooled OR, 0.68; 95% CI, 0.31 to 1.50) (Figure 53).[192, 194, 196, 197] We did not find statistical heterogeneity (I-squared = 0%). The pooled risk difference in non-fatal myocardial infarction for metformin plus a DPP-4 inhibitor versus metformin plus a sulfonylurea was -0.2% (95% CI, -0.5 to 0.2%).

Evidence on long-term cerebrovascular morbidity was mixed. One RCT reported higher rates of stroke for metformin plus a sulfonylurea compared with metformin plus a DPP-4 inhibitor;[194] another found similar rates across arms,[197] and a third reported a single event in the metformin plus sulfonylurea arm but did not report on this outcome in the metformin plus DPP-4 inhibitor arm (Table 48).[195] Of note, sulfonylurea doses were submaximal in these RCTs. (SOE: Moderate; Combination of metformin plus a DPP-4 inhibitor favored for long-term non-fatal myocardial infarction)

Table 47. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor on cardiovascular morbidity

Author, Year	Followup	Outcome	Number of Events / N (%) for Metformin + Sulfonylurea Vs. Metformin + DPP-4 Inhibitor
Nauck, 2007[192, 196]	104 weeks	MI	1/588 (0.2) vs. 0/584 (0)
Gallwitz, 2012[194]	104 weeks	Nonfatal MI	10/775 (1.3) vs. 6/776 (0.8) Unadjusted RR, 0.6; 95% CI, 0.22 to 1.64 Reference = metformin + sulfonylurea
		Composite: CV death, MI, stroke, or admission to hospital due to unstable angina	26/775 (3.4) vs. 12/776 (1.5) Unadjusted RR, 0.46; 95% CI, 0.23 to 0.91 Reference = metformin + sulfonylurea
		Admission to hospital due to unstable angina	3/775 (0.4) vs. 3/776 (0.4) Unadjusted RR, 1.0; 95% CI, 0.2 to 4.93 Reference = metformin + sulfonylurea
Del Prato, 2014[197]	104 weeks	Adjudicated non-fatal MI	4/869 (0.5) vs. 1/873 (0.1) (alogliptin 12.5 mg) 4/869 (0.5) vs. 4/878 (0.5) (alogliptin 25 mg)
Goke, 2010[195]	104 weeks	Not defined	Qualitative statement: "The incidences of CV AEs…were low and similar between treatment groups."

AE = adverse event; CI = confidence interval; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; MI = myocardial infarction; RR = risk ratio

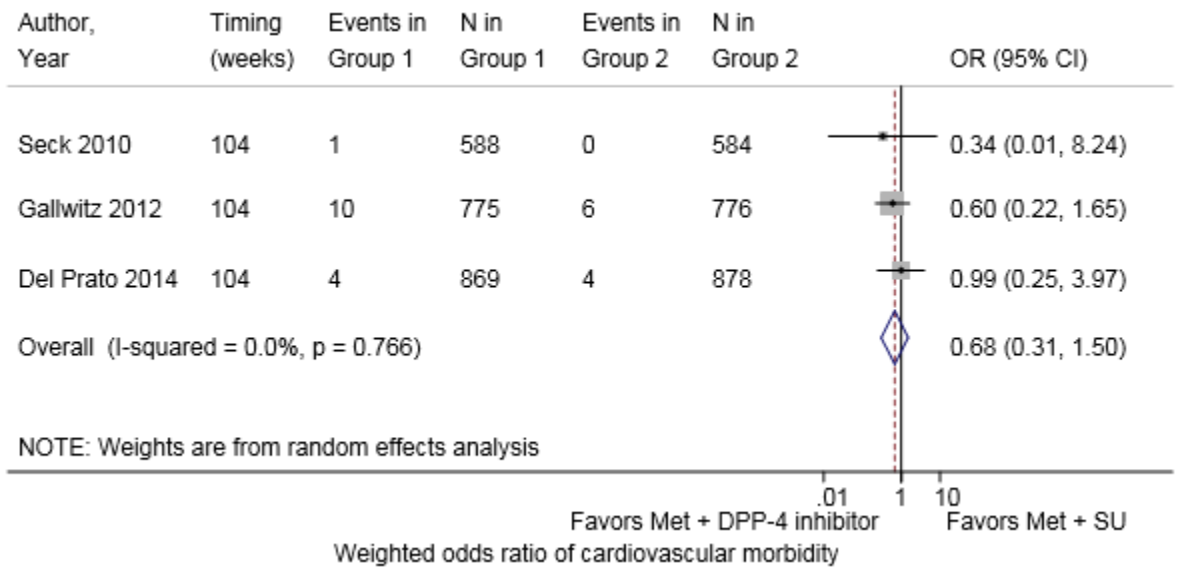
Table 48. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor on cerebrovascular morbidity

Author, Year	Followup	Outcome	Number of Events / N (%) for Metformin + Sulfonylurea Vs. Metformin + DPP-4 Inhibitor
Gallwitz, 2012[194]	104 weeks	Cerebral infarction	4/775 (0.5) vs. 0/776 (0)
		Nonfatal stroke*	11/775 (1.4) vs. 3/776 (0.4) Unadjusted RR, 0.27; 95% CI, 0.08 to 0.97 Reference = metformin + sulfonylurea
Goke, 2010[195, 248]	104 weeks	Transient ischemic attack	1/430 (0.2) vs. NR/428
Del Prato, 2014[197]	104 weeks	Adjudicated non-fatal stroke	3/869 (0.3) vs. 3/873 (0.3) (alogliptin 12.5 mg) 3/869 (0.3) vs. 2/878 (0.2) (alogliptin 25 mg)

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; NR = not reported; RR = risk ratio

* This outcome appears to include stroke and transient ischemic attacks.

Figure 53. Pooled odds ratio of cardiovascular morbidity comparing combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin plus a sulfonylurea; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

A single RCT (N=814) with 208 weeks of follow up reported no CVD events (not otherwise defined) for the combination of metformin plus glipizide or metformin plus dapagliflozin; dose of glipizide or dapagliflozin achieved was not reported.[54] (SOE: Low; Neither favored for long-term CVD morbidity)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Two short-term (26-week) RCTs (N=991) suggested no difference in cardiovascular morbidity for the combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 receptor agonist.[188, 210] One study reported no cardiovascular events in either arm (defined as unstable angina or coronary artery occlusion), and the other study reported "cardiac disorders" in one participant in the metformin plus sitagliptin and the metformin plus liraglutide 1.8 mg arm.[188, 210]

One of these trials reported on cerebrovascular accidents and reported one event in the metformin plus sitagliptin arm and no events in the metformin plus exenatide arm.[188] (SOE: Low; Neither favored for short-term cardiovascular morbidity)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a Basal Insulin

A single RCT (N=501) reported that five participants experienced cardiovascular events (carotid artery occlusion, angina pectoris, and unstable angina) in the metformin plus insulin

glargine arm (5/237, 2%) and two participants experienced cardiovascular events (nonfatal acute myocardial infarction and angina pectoris) in the metformin plus sitagliptin arm (2/264, 1%) at 25 weeks.[211] Of note, events had to be considered "serious" to be reported.[211] This study did not use an intention-to-treat analysis and had moderate, differential losses to followup across arms (5% for sitagliptin and 9% for insulin glargine).[211] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored for short-term cardiovascular morbidity)

Combination of Metformin Plus a Basal Insulin Versus a Combination of Metformin Plus a Premixed Insulin

In a 16-week cross-over study, 105 participants with newly-diagnosed type 2 diabetes were randomly assigned to metformin plus insulin glargine or metformin plus insulin lispro 75/25 twice daily.[223] During an 8-week lead-in period, participants received neutral protamine Hagedorn (NPH) insulin at night, and the metformin dose was titrated. One participant experienced a myocardial infarction during the lead-in period and one participant experienced chest pain during treatment with premixed insulin; the investigators did not report if this event occurred before or after the crossover.[223] (SOE: Insufficient)

Strength of Evidence for Cardiovascular and Cerebrovascular Morbidity

We did not find any high strength evidence for cardiovascular and cerebrovascular morbidity. Most evidence was low or insufficient because of a paucity of studies reporting on these outcomes (see Key Points, Table 49, Table 50, and Table 51). Notably, none of the RCTs was designed to evaluate cardiovascular outcomes, and the RCTs tended to be short (less than 12 months), and event rates were low. We identified a mixture of RCT and observational study evidence for these outcomes for the monotherapy comparisons, but only RCTs for combination comparisons. Most of the evidence was at medium or high risk of bias. Common study limitations included lack of reporting on randomization and masking procedures and lack of an intention-to-treat approach combined with substantial losses to followup. The consistency of this evidence was limited by the small number of studies and differences in definitions. While observational studies offer the opportunity for precision given their frequently large sizes, most evidence was still imprecise since we did not identify that many high-quality observational studies. Notably, the observational studies did not tend to corroborate RCT findings.

We identified unpublished studies for several comparisons. We identified one unpublished study describing the long-term followup (156 weeks) of one of the included studies[141] that had not reported on CVD morbidity in its publication. This study compared metformin, metformin plus a sulfonylurea, metformin plus a DPP-4 inhibitor, and metformin plus a GLP-1 receptor agonist. Rescue therapy was highest in the metformin arm (rescue therapy rates: 59, 33, 36, and 26% for the metformin, metformin plus a sulfonylurea, metformin plus a DPP-4 inhibitor, and metformin plus a GLP-1 receptor agonist arms, respectively). Given this pattern of rescue therapy (differential use of medications across arms), these unpublished findings from comparisons of combination therapies with metformin alone were dissimilar to the published results: participants in the metformin arm experienced higher rates of CVD morbidity than those in the metformin plus a sulfonylurea and metformin plus a DPP-4 inhibitor arms. This study also provided a comparison of metformin to metformin plus a GLP-1 receptor agonist, but conclusions are limited by the high and differential use of rescue therapy in this study.

We identified two short-term, unpublished studies comparing sulfonylurea with DPP-4 inhibitors which were not completely consistent with our findings (one suggested similar myocardial infarction rates but increased cerebrovascular events for sulfonylurea, and the other suggested increased risk of unstable angina for sulfonylurea users versus DPP-4 inhibitor users).

We identified two unpublished RCTs with long-term follow up comparing the combination of metformin plus a sulfonylurea with metformin plus a DPP-4 inhibitor. Results were consistent with our finding that metformin plus a DPP-4 inhibitor was associated with lower coronary heart disease risk than metformin plus a sulfonylurea. Inclusion of these studies may have raised our strength of evidence for this comparison.

We identified one published and one unpublished study of metformin plus a basal insulin versus metformin plus a premixed insulin. The published study did not report on events in both arms whereas the unpublished study suggested an increased risk of cardiovascular morbidity (consistent with the reporting of an event in the metformin plus premixed arm in the published RCT). Therefore, the unpublished study could have led to a higher grade for the strength of this evidence which might have supported a conclusion about this comparison.

Finally, we identified unpublished studies for three comparisons for which we did not have published studies. As described above, an unpublished report of the long-term follow up of an included study[141] which did not report on CVD morbidity compared metformin plus a sulfonylurea with metformin plus a GLP-1 receptor agonist and suggested that coronary heart disease risk might be higher for metformin plus a GLP-1 receptor agonist versus metformin plus a sulfonylurea. A short-term RCT comparing pioglitazone with a DPP-4 inhibitor suggested increased short-term CVD morbidity with DPP-4 inhibitor monotherapy. Another unpublished study found similar rates of cerebrovascular morbidity (cerebral infarctions) for pioglitazone and exenatide.

Table 49. Strength of evidence domains for monotherapy comparisons in terms of cardiovascular and cerebrovascular morbidity among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. rosiglitazone	RCTs: 2 (4828)	High	Inconsistent	Direct	Imprecise	Undetected	Low	Metformin favored for long-term CVD morbidity
	Observational: 3 (94,304)	Medium	Inconsistent	Direct	Precise	N/A		
Metformin vs. pioglitazone	RCTs: 3 (158)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
	Observational: 2 (58,883)	Medium	Consistent	Direct	Precise	N/A		
Metformin vs. SU	RCT: 3 (4808)	High	Inconsistent	Direct	Imprecise	Undetected	Low	Metformin favored for long-term CVD morbidity
	Observational: 6 (545,686)	Medium	Consistent	Direct	Precise	N/A		
Metformin vs. DPP-4 inhibitors	RCT: 2 (2,090)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
	Observational: 1 (84,756)	Medium	Unknown	Direct	Precise	N/A		Inadequate reporting of events in all arms
Metformin vs. SGLT-2 inhibitors	RCT: 1 (408)	High	Unknown	Direct	Imprecise	N/A	Insufficient	Unable to determine
Rosiglitazone vs. SU	RCT: 2 (4711)	High	Consistent	Direct	Imprecise	Undetected	Low	SU favored for long-term CVD morbidity
	Observational: 3 (142,502)	Medium	Inconsistent	Direct	Precise	N/A		
Pioglitazone vs. SU	RCT: 1 (502)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Pioglitazone favored for short-term CVD morbidity
	Observational: 2 (107,081)	Medium	Inconsistent	Direct	Precise	N/A		
SU vs. DPP-4 inhibitors	RCTs: 2 (653)	Medium	Consistent	Direct	Imprecise	Undetected	Low	DPP-4 inhibitor favored for short-term CVD morbidity
SU vs. GLP-1 receptor agonists	RCTs: 2 (1157)	High	Consistent	Direct	Imprecise	Undetected	Low	GLP-1 receptor agonist favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95% confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Table 50. Strength of evidence domains for metformin versus metformin-based combination comparisons in terms of cardiovascular and cerebrovascular morbidity among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + rosiglitazone (shorter duration studies)	RCTs: 7 (3136)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin favored for short-term CVD morbidity
Metformin vs. metformin + pioglitazone	RCTs: 1 (1,554)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. metformin + SU (shorter duration study)	RCT: 1 (110)	Low	Unknown	Direct	Imprecise	Undetected	Low	Metformin favored for short-term CVD morbidity
Metformin vs. metformin + DPP-4 inhibitor (shorter duration studies)	RCTs: 11 (4351)	Low	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine Inadequate reporting of events in all arms
Metformin vs. metformin + SGLT-2 inhibitor (shorter duration study)	RCT: 1 (182)	Low	Unknown	Direct	Imprecise	Undetected	Low	Metformin favored for short-term CVD morbidity

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95% confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Table 51. Strength of evidence domains for combination therapy comparisons in terms of cardiovascular and cerebrovascular morbidity among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Met + TZD vs. Met + SU	RCTs: 2 (538) Obs: 1 (80,936)	High Medium	Inconsistent Unknown	Direct Direct	Imprecise Imprecise	Undetected N/A	Insufficient	Unable to determine
Met + pioglitazone vs. Met + DPP-4 inhibitor (shorter duration studies)	RCTs: 2 (2068)	High	Consistent	Direct	Imprecise	Undetected	Low	Met + DPP-4 inhibitor favored for short-term cardiovascular morbidity
Met + rosiglitazone vs. Met + DPP-4 inhibitor (shorter duration studies)	RCTs: 2 (350)	High	Unknown	Direct	Imprecise	Undetected	Low	Met + rosiglitazone favored for short-term CVD morbidity
Met + pioglitazone vs. Met + GLP-1 receptor agonist (shorter duration study)	RCT: 1 (325)	High	Unknown	Direct	Imprecise	Undetected	Low	Met + GLP-1 receptor agonist favored for short-term CVD morbidity
Met + SU vs. Met + DPP-4 inhibitor (long-term non-fatal MI)	RCTs: 4 (5049)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Met + DPP-4 inhibitor favored for long-term non-fatal MI‡
Met + SU vs. Met + SGLT-2 inhibitor (long-term)	RCT: 1 (814)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
Met + DPP-4 inhibitor vs. Met + GLP-1 receptor agonist (short-term studies)	RCTs: 2 (1179)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Met + DPP-4 inhibitor vs. Met + basal insulin (shorter duration studies)	RCTs: 1 (501)	High	Unknown	Direct	Imprecise	Undetected	Low	Met + DPP-4 inhibitor favored for short-term CVD morbidity
Met + basal insulin vs. Met + premixed insulin	RCTs: 1 (105)	Medium	Unknown	Direct	Imprecise	Suspected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; Obs = observational; OR = odds ratio; RD = absolute risk difference; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95% confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

‡ The evidence for long-term cerebrovascular morbidity was insufficient.

Evidence for Retinopathy

Monotherapy Comparisons

Sulfonylureas Versus GLP-1 Receptor Agonists

A single RCT (N=400) compared rates of retinopathy at 52 weeks in participants randomized to submaximally dosed glibenclamide or submaximally dosed liraglutide. Nine (9/132, 6.8%) and 16 (16/268, 6%) participants were diagnosed with retinopathy as a "treatment-emergent adverse event" in the sulfonylurea and GLP-1 receptor agonist arms, respectively.[110] The study did not report on baseline rates of retinopathy.[110] Losses to follow up were greater than 15% in each arm, and the investigators did not use an intention-to-treat approach for this analysis.[110] (SOE: Low; Neither favored)

Metformin Versus a Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Two RCTs (N=437) compared low-dose metformin with low-dose metformin plus a DPP-4 inhibitor at 12 weeks and reported on retinopathy.[149, 157] Each trial reported one case of retinopathy in the metformin monotherapy arm. One of the RCTs reported one case of retinopathy in the metformin plus DPP-4 inhibitor arm (alogliptin 12.5 mg) and no cases in in the metformin plus alogliptin 25 mg arm.[157] The other RCT reported no cases in the metformin plus sitagliptin arm.[149] (SOE: Low; Neither favored short-term)

Strength of Evidence for Retinopathy

We identified three RCTs (and no observational studies) evaluating retinopathy, and one study was of poor quality.[110] Therefore, evidence is mainly insufficient for this outcome (see Key Points and Table 52). We identified an unpublished study comparing pioglitazone with exenatide which reported similar rates of blurred vision in both arms.

Table 52. Strength of evidence domains for comparisons in terms of retinopathy among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
SU vs. GLP-1 receptor agonists Shorter duration study	RCT: 1 (411)	High	Unknown	Direct	Imprecise	Undetected	Low	Neither arm favored
Metformin vs. metformin + DPP-4 inhibitors Shorter duration studies	RCTs: 2 (437)	Low	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of evidence. Unless otherwise specified, conclusions for retinopathy are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Nephropathy

We included the following nephropathy outcomes: categorical definitions of new or progressive nephropathy, changes in urine albumin, and changes in estimated glomerular filtration rate.

Studies of comparisons including a SGLT-2 inhibitor are described in the section on renal insufficiency in this report (see Key Question 3 – renal insufficiency).

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

One RCT and two retrospective cohort studies evaluated this outcome and found mixed results.[62, 249, 250] The 12-month RCT (N=1,194) reported a significant decrease in the urine albumin-to-creatinine ratio for participants randomized to the pioglitazone arm compared with the metformin arm (19% versus 1% reduction; $P = 0.002$).[62]

The smaller retrospective cohort study of 1,271 patients in the US (Baylor Health Care System, Dallas, TX and Christiana Care Health System, Newark, DE) evaluated nephropathy defined as new albuminuria or new estimated glomerular filtration rate (eGFR) rate below 60 mL/min/1.73 m^2 and found no significant difference between metformin users and thiazolidinedione users, for either outcome (adjusted HR, 1.00 and 1.04 for thiazolidinedione versus metformin), with median followup of 2.8 to 3.2 years.[250]

The large, although short, retrospective cohort study from the Veterans Health Administration (N=93,577) with median followup of 0.7 to 0.9 years also found no significant difference in nephropathy for thiazolidinedione versus metformin users. The adjusted HR for the composite outcome of an eGFR event (persistent decline of 25% or greater from baseline eGFR) or end-stage renal disease (eGFR less than 15 mL/min/1.73 m^2or first inpatient or outpatient code for dialysis or related procedures or renal transplant) was 0.92 (95% CI, 0.71 to 1.18).[249] (SOE: Insufficient)

Metformin Versus Sulfonylureas

One small (N=51) 3-month RCT reported that microalbuminuria decreased significantly with metformin ($P = 0.008$) and increased non-significantly with glibenclamide ($P = 0.09$). eGFR was stable in the metformin arm ($P = 0.46$) and increased in the sulfonylurea arm ($P = 0.04$).[251] The study did not provide statistical comparisons between groups.

Three retrospective cohort studies in the United States suggested a decreased risk of nephropathy among metformin versus sulfonylurea users (Table 53).[249, 250, 252] Two of the studies were from the Veterans Health Administration and it is not clear if the study populations overlapped.[249, 252] (SOE: Low; Metformin favored)

Table 53. Retrospective cohort studies comparing metformin with sulfonylureas on nephropathy

Author, Year	Population	Followup	Outcome Definition	HR (95% CI)
Hung, 2013[252]	Veterans Health Administration VA Mid-South VISN 9 Data Warehouse (N=13,238) Incident medication users	Approximately 1 year	Composite of GFR event or ESRD*	All: 0.85 (0.72 to 1.01) Urine protein measures at baseline: 0.78 (0.64 to 0.97) Reference = sulfonylurea
Hung, 2012[249]	Veterans Health Administration N=93,577 Did not appear to exclude incident users	0.7 to 0.9 years (median)	Composite of GFR event or ESRD*	1.2 (1.13 to 1.28) Reference = metformin
Masica, 2013[250]	1,271 participants from an electronic health record database in the US (Baylor Health Care System, Dallas, TX) and Christiana Care Health System, Newark, DE)	Median follow up of 2.8 to 3.2 years	Microalbuminuria or worse	Urine protein measures available: 1.27 (0.93 to 1.74) Reference = metformin
			eGFR ≥60 ml/min/1.73m^2 at first measurement and an eGFR <60 ml/min/1.73m^2 during follow-up	eGFR available: 1.41 (1.05 to 1.91) Reference = metformin

CI = confidence interval; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio; ml/min/1.73m^2 = milliliters per minute per 1.73 meters squared; VA = Veterans Affairs; VISN = Veterans Integrated Service Network

* GFR event= persistent 25% or greater decline from the baseline eGFR; ESRD: eGFR <15 mL/minute/1.73m2 or first code for dialysis or related procedure or renal transplant

Thiazolidinediones Versus Sulfonylureas

Five small RCTs provided mixed results on the effect of thiazolidinediones and sulfonylureas on nephropathy outcomes, and all studies reported on albuminuria as the outcome.[96-98, 102, 253] Four trials found less albuminuria in patients receiving pioglitazone compared with a sulfonylurea;[96, 97, 102, 253] only one reported a significant difference.[96] One trial compared rosiglitazone and glyburide at 12 months and found no statistically significant difference in the urinary albumin-to-creatinine ratio; progression to microalbuminuria did not differ between groups.[98]

A retrospective cohort study using a small US database reported a non-significant increased risk of nephropathy (incident albuminuria) among sulfonylurea versus thiazolidinedione users who had a measure of urine protein (adjusted HR, 1.27; 95% CI, 0.93 to 1.74).[250] (SOE: Low; Thiazolidinediones favored)

Sulfonylureas Versus DPP-4 Inhibitors

A single RCT analyzed changes in eGFR and urine albumin-to-creatinine ratio from baseline among 277 participants randomized to glipizide or sitagliptin.[107] Over 54 weeks, the eGFR decreased slightly in both arms (-3.3 and -3.9 ml/min/1.73m^2 for glipizide and sitagliptin, respectively) and urine albumin-to-creatinine ratio increased slightly in both arms (0.1 and 0.06 for glipizide and sitagliptin, respectively). Of note, approximately 20 percent of participants were

lost to followup in each arm (423 participants originally randomized), and the investigators did not conduct an intention-to-treat analysis. (SOE: Low; Neither favored)

Sulfonylureas Versus GLP-1 Receptor Agonists

A single RCT (N=745) reported similar cumulative incidences of 6 percent, 5 percent and 5 percent of "renal and urinary disorders" at 104 weeks in patients randomized to glimepiride 8 mg, liraglutide 1.2 mg, and liraglutide 1.8 mg.[113] (SOE: Low; Neither favored)

DPP-4 Inhibitors Versus GLP-1 Receptor Agonists

A single small RCT with 24 weeks of followup compared sub-maximal sitagliptin (50 mg) to sub-maximal liraglutide (0.9 mg daily) and reported negligible changes in eGFR and urinary albumin excretion in both arms.[115] (SOE: Low; Neither favored for short-term nephropathy outcomes)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Two RCTs compared metformin plus rosiglitazone with metformin plus a sulfonylurea. Evaluation of the urine albumin-to-creatinine ratio favored the combination of metformin plus rosiglitazone.[177, 182] One small RCT (N=34), with 48 weeks of followup, reported a negligible decrease in urine albumin-to-creatinine ratio in the metformin plus thiazolidinedione arm (-0.77 mg/g) and a small increase (12.2 mg/g) in the metformin plus sulfonylurea arm.[182] The larger trial (N=389) reported a greater, although non-significant, reduction in the urine albumin-to-creatinine ratio with the combination of metformin plus a thiazolidinedione versus metformin plus a sulfonylurea arm, at 32 weeks.[177]

The smaller RCT also reported a negligible decrease in eGFR in the metformin plus thiazolidinedione arm (-1.48 ml/min/1.73m^2) and an increase in eGFR in the metformin plus sulfonylurea group (9.97 ml/min/1.73m^2); the study did not provide a statistical comparison of the between-group difference.[182] This very small trial reported more than 20 percent losses to followup across arms and did not use an intention-to-treat analysis for nephropathy.[182] (SOE: Low; Combination of metformin plus a thiazolidinedione favored)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a DPP-4 Inhibitor

A single RCT (N=514) with 26 weeks of followup reported on percent change in urine albumin-to-creatinine ratio for the combination of metformin plus pioglitazone and the combination of metformin plus sitagliptin and found similar changes from baseline in both arms: -4% (95% CI, -17% to 12.1%) for metformin plus pioglitazone and -6.9% (95% CI, -20% to unclear but greater than 0%) for metformin plus sitagliptin.[188] This study had 13 percent and 21 percent losses to followup in the sitagliptin- and pioglitazone-based arms, respectively, and did not use an intention-to-treat analysis for this outcome.[188] (SOE: Low; Neither treatment favored)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

A single RCT (N=514) with 26 weeks of followup reported on percent change in urine albumin-to-creatinine ratio for the combination of metformin plus pioglitazone and the combination of metformin plus exenatide and found a reduction in urine albumin-to-creatinine from baseline for the metformin plus exenatide arm [-16% (95% CI, -28% to -2%)] and no significant reduction for the metformin plus pioglitazone arm [-4% (95% CI, -17% to 12%)].[188] This study had approximately 20 percent losses to followup in both arms and did not use an intention-to-treat analysis for this outcome.[188] (SOE: Low; Combination of metformin plus a GLP-1 receptor agonist favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

A small RCT conducted in 42 participants with baseline microalbuminuria compared change in 24-hour urine albumin over 16 weeks for metformin plus sub-maximally dosed glimepiride and metformin plus exenatide. The authors reported a significant reduction in urine albumin in the metformin plus exenatide arm (-42 mg/day; *P* for change for baseline <0.01) compared to the metformin plus glimepiride arm (5 mg/day; *P* for change from baseline >0.05; calculated between group difference, -37 mg/day; *P* for between-group difference <0.001).[202] This small study had more than 20 percent losses to followup across arms and did not use an intention-to-treat analysis.[202] (SOE: Low; Combination of metformin plus a GLP-1 receptor agonist favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

A single RCT (N=514) with 26 weeks of followup reported on percent change in urine albumin-to-creatinine ratio for the combination of metformin plus sitagliptin and the combination of metformin plus exenatide.[188] The trial found a statistically significant reduction in urine albumin-to-creatinine from baseline for the metformin plus exenatide arm (-16%; 95% CI, -28% to -2%) but not for the metformin plus sitagliptin arm (-6.9%; 95% CI, -20% to unclear but greater than 0%).[188] This study had approximately 20 percent losses to followup in both arms and did not use an intention-to-treat analysis for this outcome.[188] (SOE: Low; Combination of metformin plus a GLP-1 receptor agonist favored)

Strength of Evidence for Nephropathy

We found low or insufficient strength of evidence on nephropathy outcomes for all comparisons of interest as described in the Key Points, Table 54, and Table 55.

The evidence on nephropathy was limited by the lack of studies. For RCTs, major study limitations included small sample sizes and high rates of withdrawals (>20%), without use of an intention-to-treat approach. We could usually not determine consistency because of a lack of studies, and the evidence on all comparisons was imprecise because of insufficient sample size. We did not detect reporting bias. However, the small number of studies limited our ability to assess publication bias. Many of the studies did not provide measures of dispersion for nephropathy outcomes, but we did not believe that this was actually a source of selective analysis reporting bias as much as a reflection of a lack of a focus on reporting of these outcomes given that they were not primary outcomes.

Table 54. Strength of evidence domains for monotherapy comparisons in terms of nephropathy among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. TZD	RCT: 1 (1194) Observational: 2 (94,848)	Low Medium	Unknown Inconsistent	Direct Direct	Imprecise Precise	Undetected N/A	Insufficient	Unable to determine
Metformin vs. SU (shorter duration studies)	RCT: 1 (51) Observational: 3 (108,356)	High Medium	Unknown Consistent	Indirect Direct	Imprecise Precise	Undetected N/A	Low	Metformin favored
TZD vs. SU (mainly shorter duration studies)	RCTs: 5 (308) Observational: 2 (1271)	High Medium	Consistent Unknown	Direct Direct	Imprecise Imprecise	Undetected N/A	Low	TZD favored for short-term nephropathy outcomes
SU vs. DPP-4 inhibitors (shorter duration study)	RCT: 1 (423)	High	Unknown	Indirect	Imprecise	Undetected	Low	Neither treatment favored
SU vs. GLP-1 receptor agonists (longer duration study)	RCT: 1 (746)	Medium	Unknown	Indirect	Imprecise	Undetected	Low	Neither treatment favored
DPP-4 inhibitors vs. GLP-1 receptor agonists (shorter duration study)	RCT: 1 (56)	High	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; N/A = not applicable; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Studies of comparisons including an SGLT-2 inhibitor are graded in the section on renal insufficiency in this report. Unless otherwise specified, conclusions for nephropathy are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Table 55. Strength of evidence domains for metformin-based combination comparisons in terms of nephropathy among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + TZD vs. metformin + SU (shorter duration studies)	RCT: 2 (433)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin + TZD favored
Metformin + TZD vs. metformin + DPP-4 (shorter duration study)	RCT: 1 (514)	High	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin + TZD vs. metformin + GLP-1 receptor agonist (shorter duration study)	RCT: 1 (514)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 favored
Metformin + SU vs. metformin + GLP-1 receptor agonist (shorter duration study)	RCT: 1 (42)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 favored
Metformin + DPP-4 inhibitor vs. metformin + GLP-1 receptor agonist	RCT: 1 (514)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Studies of comparisons including an SGLT-2 inhibitor are graded in the section on renal insufficiency in this report. Unless otherwise specified, conclusions for nephropathy are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Neuropathy

For the neuropathy analyses, we included studies where newly developed neuropathy was reported for each treatment group. Four short trials reported on neuropathy as an adverse outcome.[121, 142, 154, 183]

Monotherapy Comparisons

Metformin Versus DPP-4 Inhibitors

A single RCT compared the effects of metformin with alogliptin on undefined neuropathy. At 26 weeks of followup, one participant developed unspecified neuropathy in each of the alogliptin arms [12.5 mg (n=213) and 25 mg (n=210)]); neuropathy was not reported on in the metformin arm.[154] (SOE: Insufficient)

Metformin Versus a Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

In a single RCT of 26 weeks duration, one withdrawal owing to undefined neuropathy occurred in the metformin arm (n=34); no events were reported on in the two metformin plus rosiglitazone arms (n=35 and n=36).[121] (SOE: Insufficient)

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

One RCT reported the occurrence of undefined diabetic neuropathy as 2.1 percent among participants in the metformin arm (n=94) and 4.2 percent in the metformin plus sitagliptin arm (n=96) at 30 weeks.[142] (SOE: Low; Metformin favored)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

In a 6-month trial, neuropathy was described but was not a pre-specified outcome.[183] One of 103 participants in the metformin plus thiazolidinedione arm developed neuropathy, and none of the 80 participants in the metformin plus sulfonylurea arm developed neuropathy.[183] (SOE: Low; Neither favored)

Strength of Evidence for Neuropathy

The evidence grading for neuropathy is summarized in Table 56.

Table 56. Strength of evidence domains for comparisons in terms of neuropathy among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. DPP-4 inhibitors	RCT: 1 (527)	Low	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine Results not reported for all arms
Metformin vs. metformin + TZD	RCT: 1 (105)	Medium	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine Results not reported for all arms
Metformin vs. metformin + DPP-4 inhibitor (shorter duration study)	RCT: 1 (190)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin favored
Metformin + TZD vs. metformin + SU (shorter duration study)	RCT: 1 (183)	High	Unknown	Indirect	Imprecise	Undetected	Low	Neither treatment favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for neuropathy are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Key Questions 3a and 3b: Safety

Study Design and Population Characteristics

We included 145 studies describing adverse effects for the comparisons of interest (Appendix D, Tables D10 to D13). We included 64 articles from our prior 2011 review[16] and identified an additional 81 studies for this update. Six of the newly-included studies were updates of earlier studies.[85, 87, 110, 113, 196, 210] The majority were RCTs (62 from the previous report and an additional 75 for the update). Most of the RCTs (109 out of 137, 80%) lasted 1 year or less. Sixteen RCTs (12%) had at least 2 years of followup. Few studies were designed explicitly to evaluate adverse events. Of the 22 studies designed to evaluate the adverse events specified in Key Question 3, most focused on cancer[254, 255] and renal toxicity.[249, 252] Thirty-one of 81 RCTs (38%) did not report on the use of rescue therapy; rescue therapy was allowed in 29 studies (36%) and was disallowed in 21 studies (26%).

The mean age of participants ranged from approximately 40 years to 81 years, with the majority of studies reporting a mean age in the upper 50s. About 50 percent of the participants were female. Sixty-two studies did not report race or ethnicity. In the studies that reported race, the majority of the participants were Caucasians. No study included more than 25 percent African American participants; two studies included more than 70 percent Hispanic participants[121, 186] and seven studies included more than 70 percent Asian participants.[74, 92, 109, 155, 160, 254, 256]

Risk of Bias

We included 137 trials in this section**.** All of the trials were described as randomized. Fifty-one percent of the trials described their randomization scheme, and another 65 percent of the trials were described as being double-blinded. Thirty-six percent of all double-blinded RCTs also described the steps taken to ensure blinding. The majority of trials (86 percent) described the withdrawals and dropouts. Of the 16 RCTs with at least 2 years of followup, 12 had over 20% loss to followup.

Of the eight observational studies included for this Key Question, 88 percent reported actual probability values and 63 percent described their measurement of the outcomes of interest. All studies described and adjusted for confounding factors and conducted statistical analyses. Seventy-five percent of studies described the number of participants who were lost to followup after the start of the period of observation.

Key Points and Evidence Grades

Hypoglycemia

Mild, Moderate, or Total Hypoglycemia

Unless otherwise noted, results on hypoglycemia refer to the number of participants experiencing hypoglycemia and not to the number of events.

- Metformin monotherapy was favored over the following:
  - Sulfonylurea monotherapy for mild-moderate hypoglycemia (pooled OR for sulfonylurea versus metformin, 4.00; 95% CI, 1.75 to 9.83) (SOE: High)

    - The combination of metformin plus a thiazolidinedione (pooled OR for metformin plus a thiazolidinedione versus metformin monotherapy for total hypoglycemia, 1.56; 95% CI, 0.99 to 2.44) (SOE: Moderate)
    - The combination of metformin plus a sulfonylurea for mild, moderate, or total hypoglycemia (range in ORs, 2.15 to 28.6) (SOE: Moderate)
    - The combination of metformin plus an SGLT-2 inhibitor for mild or moderate hypoglycemia (pooled OR, 1.74; 95% CI, 0.83 to 3.66) (SOE: Moderate)
- The risks of mild-moderate and total hypoglycemia were similar for metformin monotherapy and the combination of metformin plus a DPP-4 inhibitor. (SOE: High)
    - Pooled OR for metformin plus a DPP-4 inhibitor versus metformin monotherapy:
        - Mild-moderate hypoglycemia: 0.97; 95% CI, 0.63 to 1.51
        - Total hypoglycemia: 0.96; 95% CI, 0.55 to 1.67
- Sulfonylurea monotherapy increased the risk of total hypoglycemia compared with thiazolidinedione monotherapy (pooled OR 6.31; 95% CI, 4.08 to 9.76). (SOE: High)
- SGLT-2 inhibitor monotherapy was associated with a lower risk of hypoglycemia compared with metformin monotherapy (pooled OR, 0.46; 95% CI, 0.16 to 1.30). (SOE: Moderate)
- DPP-4 inhibitor monotherapy was favored over sulfonylurea monotherapy (range of OR, 0.08 to 0.26 from individual studies for sulfonylurea versus DPP-4 inhibitor monotherapy). (SOE: Moderate)
- Mild-moderate hypoglycemia was more common with sulfonylurea monotherapy than with GLP-1 receptor agonist monotherapy (range in OR, 3.2 to 5.3). (SOE: Moderate)
- When compared with metformin plus a sulfonylurea, metformin plus an SGLT-2 inhibitor had less risk of mild or moderate hypoglycemia (range in OR, 0.03 to 0.13). (SOE: High)
- When compared with metformin plus sulfonylurea, several combinations had less risk of mild, moderate, or total hypoglycemia: metformin plus a thiazolidinedione, metformin plus a DPP-4 inhibitor, and metformin plus a GLP-1 receptor agonist (range in OR, 0.07 to 0.19). (SOE: High or Moderate for all comparisons)
- When compared with metformin plus basal insulin or premixed insulin, metformin plus a GLP-1 receptor agonist had less risk of mild or moderate hypoglycemia (range in OR, 0.18 to 0.35). (SOE: Moderate)
- Moderate grade evidence showed a lower risk of hypoglycemia when metformin is combined with a basal insulin rather than a premixed insulin (range in OR, 0.23 to 0.89).

Severe Hypoglycemia

- Only the sulfonylurea comparisons convincingly demonstrated an increased risk of severe hypoglycemia in the sulfonylurea arms compared with nonsulfonylurea medications:
    - Sulfonylurea versus metformin (range in OR, 1.41 to 2.04) (SOE: Moderate)
    - Sulfonylurea versus thiazolidinediones (OR, 8.1) (SOE: Moderate)
    - Metformin plus sulfonylurea versus metformin plus SGLT-2 inhibitors, and metformin plus sulfonylurea versus metformin plus DPP-4 inhibitors. (SOE: Moderate or High)

Gastrointestinal (GI) Side Effects

- GI adverse events are more common with:

    - Metformin than with DPP-4 inhibitors (pooled OR 2.6 and 2.7 for diarrhea and nausea, favoring DPP-4 inhibitors), (SOE: High);
    - Metformin than thiazolidinediones (between 1.7 to 4.2 fold higher odds), (SOE: Moderate);
    - Metformin than sulfonylureas (between 2.2 to 2.4 fold higher odds), (SOE: Moderate);
    - GLP-1 receptor agonists than metformin for nausea and vomiting (between 1.3 to 1.7 fold increased odds with GLP-1 receptor agonists). (SOE: Moderate)
    - GLP-1 receptor agonists than sulfonylureas (between 1.5 to 2.4 fold higher odds of diarrhea), (SOE: Moderate)
    - Metformin plus a GLP-1 receptor agonist than metformin plus a DPP-4 inhibitor (between 1.0 to 7.8 fold higher odds with metformin plus GLP-1 receptor agonists), (SOE: Moderate);
    - Metformin plus a GLP-1 receptor agonist than metformin plus a thiazolidinedione (between 2.9 to 6.3 fold higher odds with metformin plus a GLP-1 receptor agonist). (SOE: Moderate)
- GI adverse events are equally common with:
    - Thiazolidinediones and sulfonylureas (SOE: High)
    - Metformin monotherapy and metformin plus a DPP-4 inhibitor (SOE: Moderate for any GI adverse event, nausea, and vomiting for shorter duration studies)
    - Metformin plus a sulfonylurea and metformin plus a DPP-4 inhibitor in longer studies (SOE: High)
    - Metformin monotherapy and combination therapy with metformin plus a SGLT-2 inhibitor (for diarrhea) (SOE: Moderate)
    - Metformin plus a thiazolidinedione and metformin plus a sulfonylurea. (SOE: Moderate)

Cancer

- Type of cancer was not designated a priori in most of the studies reporting on cancer; thus, the following conclusions apply to any cancer, unless specified.
- Even though the FDA has issued warnings regarding increased risk of bladder cancer risk with pioglitazone, we found low or insufficient strength of evidence on TZD-based comparisons and cancer outcomes.
- Despite FDA warnings of a possible increased risk of thyroid cancer with GLP-1 receptor agonists, we found low-strength or insufficient evidence on GLP-1 receptor agonist-based comparisons and cancer outcomes.

Congestive Heart Failure

- Thiazolidinediones alone increase the risk of heart failure when compared with sulfonylureas (pooled OR in four RCTs of 1.6; 95% CI, 0.96 to 2.8) or metformin (two RCTs lasting less than a year with no events, one 4-year RCT with an absolute risk difference of 3% and range in HR of 1.2 to 1.5 in two observational studies with 6 to 8 years of followup). (SOE: Low)
- Despite recent concerns of congestive heart failure with DPP-4 inhibitors, we found low or insufficient strength of evidence on the comparative safety of this drug class for this outcome.

Pancreatitis

- Despite FDA warnings regarding an increased risk of pancreatitis with GLP-1 receptor agonists and DPP-4 inhibitors, we found low or insufficient evidence on the comparative safety of these drug classes for this outcome.

Genital Mycotic Infections (for Comparisons That Include SGLT-2 Inhibitors)

- Compared with metformin monotherapy, genital infection rates were higher for SGLT-2 inhibitor monotherapy and for the combination of metformin plus an SGLT-2 inhibitor. Rates of genital infections for combination therapy with metformin plus an SGLT-2 inhibitor were higher compared to the following:
  - Metformin monotherapy: pooled OR for women, 3.0; 95% CI, 1.2 to 7.2 and pooled OR for men, 2.7; 95% CI, 0.8 to 9.0 (SOE: High)
  - Metformin plus a sulfonylurea: pooled OR for women, 5.2; 95% CI, 3.4 to 7.8; pooled OR for men, 7.6; 95% CI, 4.0 to 14.4 (SOE: High)
  - Metformin plus a DPP-4 inhibitor

Other Serious Adverse Events

- There was no moderate or high strength of evidence for the following adverse events: liver injury, lactic acidosis, severe allergic reactions, macular edema/decreased vision, urinary tract infections (for SGLT-2 inhibitors) impaired renal function (for SGLT-2 inhibitors), fractures (for SGLT-2 inhibitors), and volume depletion (for SGLT-2 inhibitors). Therefore, we were unable to draw any firm conclusions regarding the diabetes medication comparisons and these safety outcomes.

Evidence for Hypoglycemia

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Five RCTs addressed hypoglycemia for metformin versus thiazolidinediones, finding no consistent differences in hypoglycemia by arm (Table 57).[50, 70, 71, 73, 74] We were unable to conduct a meta-analysis because of differences in the definitions of hypoglycemia and lengths of followup. (SOE: Low; Metformin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 57. Randomized controlled trials comparing metformin with thiazolidinediones on hypoglycemia

Author, Year	Followup	Metformin (Dose*)	TZD (Dose*)	Definition of Hypoglycemia	Results† (Metformin Vs TZD)
Kahn, 2006[50]	4 years	Metformin (max 2000 mg)	Rosiglitazone (max 8 mg)	Total (self-reported)	168/1454 (11.6%) vs 142/1456 (9.8%)
Yoon, 2011[74]	48 weeks	Metformin (max 2000 mg; mean 1234.2 mg)	Rosiglitazone (max 8 mg; mean 5.9 mg)	Total (signs or symptoms)	4/114 (3.5%) vs 8/117 (6.8%)
Erem, 2014[70]	48 weeks	Metformin (max 2000 mg)	Pioglitazone (max 45 mg)	Total (not specified)	0/19 (0%) vs 0/19 (0%)
Russell-Jones, 2012[73]	26 weeks	Metformin (max 2500 mg)	Pioglitazone (max 45 mg)	Severe‡ Total (signs or symptoms)	0/246 (0%) vs 0/163 (0%) 10/246 (4.1%) vs 6/163 (3.7%)
Genovese, 2013[71]	16 weeks	Metformin (max 2550 mg)	Pioglitazone (max 45 mg)	Total (not specified)	0 episodes among 26 patients vs 4 episodes among 24 patients

Max = maximum; mg = milligram; TZD = thiazolidinedione
* All doses were titrated, unless otherwise stated.
† Results are presented as n/N (%) unless otherwise stated.
‡ Severe hypoglycemia was defined as symptoms resulting in loss of consciousness or seizure that showed prompt recovery after glucose administration, or documented blood glucose less than 3.0 mmol/L that required the assistance of another person because of severe impairment in consciousness.

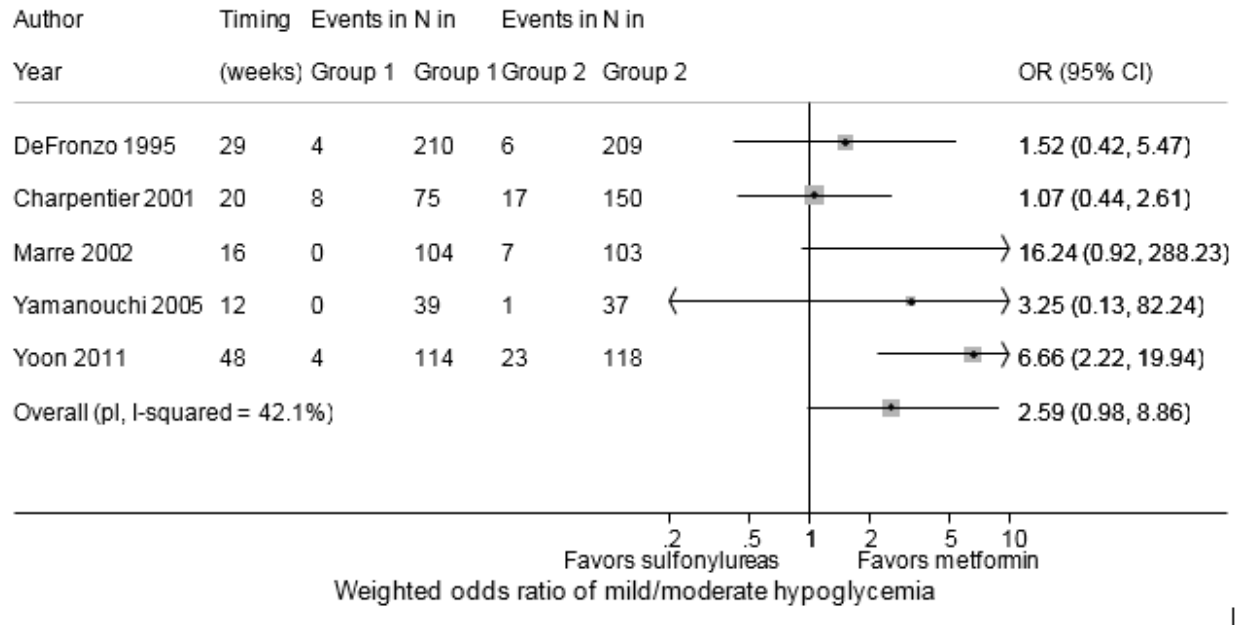
Metformin Versus Sulfonylureas

Fifteen studies addressed this comparison (14 RCTs and one observational study).[50, 60, 74, 129, 131-134, 136-138, 231, 257-259] Meta-analysis of five short-term RCTs deemed sufficiently homogeneous for quantitative synthesis suggested an increased risk of mild to moderate hypoglycemia for sulfonylureas versus metformin (pooled OR, 2.59; 95% CI, 0.98 to 8.86) (Figure 54). Exclusion of any one study did not change this inference.

We did not include several studies in the meta-analysis because of differences in hypoglycemia definitions,[131, 133, 134, 231] in study duration,[50, 258] in how hypoglycemic events were reported,[258] dosing of SU,[129] and in study design.[259] We did not include two studies in the meta-analysis of relative odds because neither had any events in either arm.[138, 257] Results of the studies not included in the meta-analyses were consistent with the findings of the meta-analysis showing an increased risk of hypoglycemia for sulfonylurea versus metformin monotherapy (Table 58). Based on limited data to evaluate this, rates of hypoglycemia did not appear to be higher for the glyburide compared to other sulfonylurea arms across the studies.

Three studies (two RCTs and one observational study) reported on severe hypoglycemia (range in OR 0.49 to 0.71; range in RD -1% to -23%), all favoring metformin (Table 58).[134, 231, 259] (SOE: High; Metformin favored for mild, moderate, or total hypoglycemia) (SOE: Moderate; Metformin favored for severe hypoglycemia)

Figure 54. Pooled odds ratio of mild or moderate hypoglycemia comparing metformin with sulfonylureas



CI = confidence interval; Group 1 = metformin; Group 2 = sulfonylureas; OR = odds ratio; pl = profile likelihood estimate
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The line at the bottom of the graph indicates the 95 percent confidence interval for the profile likelihood pooled estimate.

Table 58. Studies comparing metformin with sulfonylureas for hypoglycemia

Author, Year Study Design	Followup	Metformin (Dose in mg*)	SU (Dose in mg*)	Definition of Hypoglycemia	Results† (Metformin Vs SU)
Hermann, 1994[134] RCT	24 weeks	Metformin (max 3000)	Glyburide (max 14)	Severe (based on clinical findings or available BG)	8/38 (21.1%) vs 12/34 (35.3%); *P* = 0.18
Hong, 2013[231] RCT	36 months	Metformin (max 1500; mean 1400)	Glipizide (max 30; mean 28.3)	Severe (required assistance and/or PG < 56 mg/dL [3.1 mmol/L])	3/156 (1.9%) vs 4/148 (2.7%)
Chien, 2007[138] RCT	16 weeks	Metformin (max 2000; mean 1910)	Glyburide (max 20; mean 19)	Mild-moderate (symptomatic or BG < 60 mg/dL)	0/25 (0%) vs 0/23 (0%)
Blonde, 2002[131] RCT	16 weeks	Metformin (max 2000)	Glyburide (fixed at 10)	Symptomatic and FSG <= 60 mg/dL	1/153 (1%) vs. 3/164 (2%)
Garber, 2003[129] RCT	16 weeks	Metformin (max 2000)	Glyburide (max 10)	Symptoms suggesting hypoglycemia	29/164 (18%) vs. 98/151 (65%)
Marre‡, 2002[132] RCT	16 weeks	Metformin (max 2000)	Glibenclamide (max 20)	Symptoms or labs	0/104 (0%) vs. 7/103 (7%)
Garber, 2002[133] RCT	20 weeks	Metformin (max 2000)	Glyburide (max 10)	Symptomatic and BG < 60 mg/dL	0/159 (0%) vs. 10/160 (6%)
DeFronzo‡, 1995[137] RCT	29 weeks	Metformin (max 2500)	Glyburide (max 20)	Not reported	4/210 (2%) vs. 6/209 (3%)
Kahn, 2006[50] RCT	4 years	Metformin (max 2000)	Glyburide (max 15)	Total (self-reported)	168/1454 (11.6%) vs 557/1441 (38.7%)
Wright, 2006[258] RCT	6 years	Metformin (max 2550)	Glyburide (max 20)	Mild to severe (not just transient symptoms)	Mean annual percentage 0.3% among 290 patients vs 1.2% among 1418 patients
Yamanouchi‡, 2005[60] RCT	12 weeks	Metformin (fixed at 750)	Glimepiride (max 2)	Not reported	0/39 (0%) vs. 1/37 (3%)
Charpentier‡, 2001[136] RCT	20 weeks	Metformin (fixed at 2550)	Glimepiride (max 6)	Symptomatic	8/75 (11%) vs. 17/150 (11%)
Derosa, 2004[257] RCT	48 weeks	Metformin (max 3000)	Glimepiride (max 4)	Mild-moderate (not specified)	0/75 (0%) vs 0/73 (0%)
Yoon‡, 2011[74] RCT	48 weeks	Metformin (mean 1234.2; max 2000)	Glimepiride (mean 4.5; max: 8)	Symptomatic	4/114 (4%) vs. 23/118 (19%)
Weir, 2011[259] Retrospective cohort	3 months	Metformin (NR)	Glyburide (NR)	Total (presented to an emergency room or hospital with an admission diagnosis of hypoglycemia)	Among patients with normal renal function 27/572 (4.7%) vs 53/193 (27.5%); aOR = 9.0 (95% CI, 4.9 to 16.4) Among patients with impaired renal function 29/580 (5.0%) vs 109/444 (24.5%); aOR = 6.0 (95% CI, 3.8 to 9.5)

aOR = adjusted odds ratio; BG = blood glucose; CI = confidence interval; max = maximum; mg = milligrams; mg/dL = milligrams per deciliter; mmol/L = millimoles per liter; PG = plasma glucose; RCT = randomized controlled trial; SU = sulfonylurea

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.
‡ Results were included in the meta-analysis.

Metformin Versus DPP-4 Inhibitors

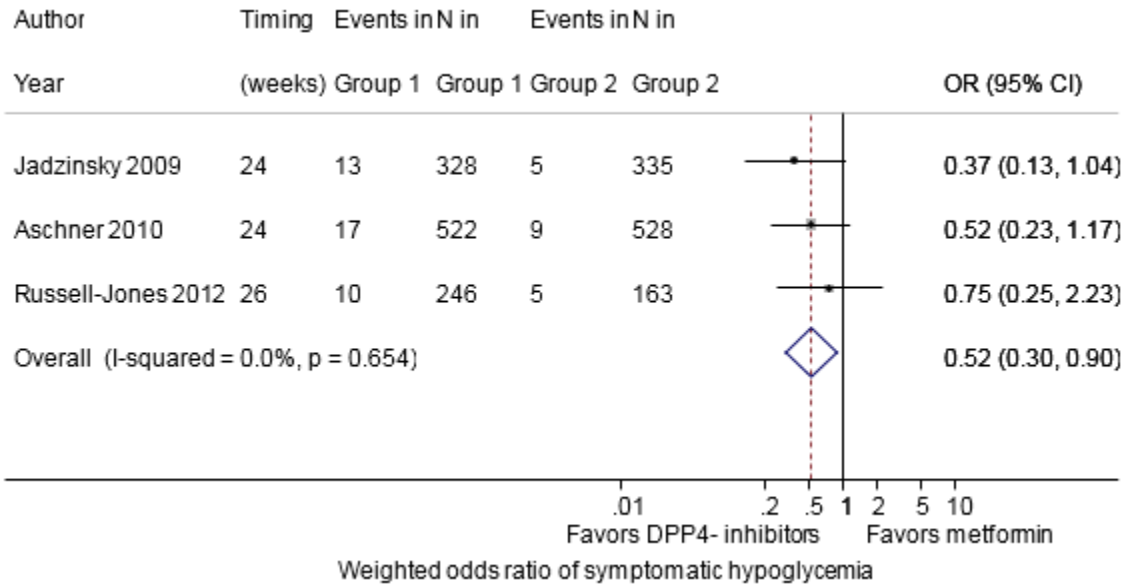
Six RCTs (reported in seven publications) compared metformin with DPP-4 inhibitors and reported on hypoglycemia.[73, 82-87]

Meta-analysis of the short-term, sufficiently-homogeneous RCTs favored DPP-4 inhibitors over metformin for symptomatic hypoglycemia (pooled OR, 0.52; 95% CI, 0.30 to 0.90) (Figure 55).[73, 82, 83] Consistent with these findings, longer-term followup from two studies also revealed less hypoglycemia in the DPP-4 inhibitor arms compared with the metformin arms.[85, 87] Of note, differences in hypoglycemia rates across the arms were not as clear when the definition of hypoglycemia required biochemical confirmation.[73, 84]

Rates of severe hypoglycemia were low in the studies reporting on this outcome. Of four short RCTs (24 to 26 weeks), two reported no severe hypoglycemia in either arm.[73, 84] One study reported a single event in the metformin arm and none in the DPP-4 inhibitor arm,[86] and the other study reported two events in the DPP-4 inhibitor arm and did not report on severe hypoglycemia in the metformin arm.[82] Of two RCTs with long-term followup (76 to 104 weeks), one reported no severe hypoglycemia events,[87] and the other reported three events of severe hypoglycemia in the metformin monotherapy arms (n=2 for metformin 1000 mg and n=1 for metformin 2000 mg daily) and none in the DPP-4 inhibitor arm.[85]

Three of the six RCTs did not use an intention-to-treat approach, and withdrawals were high in all three of these studies,[83-85] with two excluding data from persons initiating rescue therapy.[83, 84] (SOE: Low; DPP-4 inhibitors favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Figure 55. Pooled odds ratio of symptomatic hypoglycemia comparing metformin with DPP-4 inhibitors



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = dipeptidyl peptidase-4; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

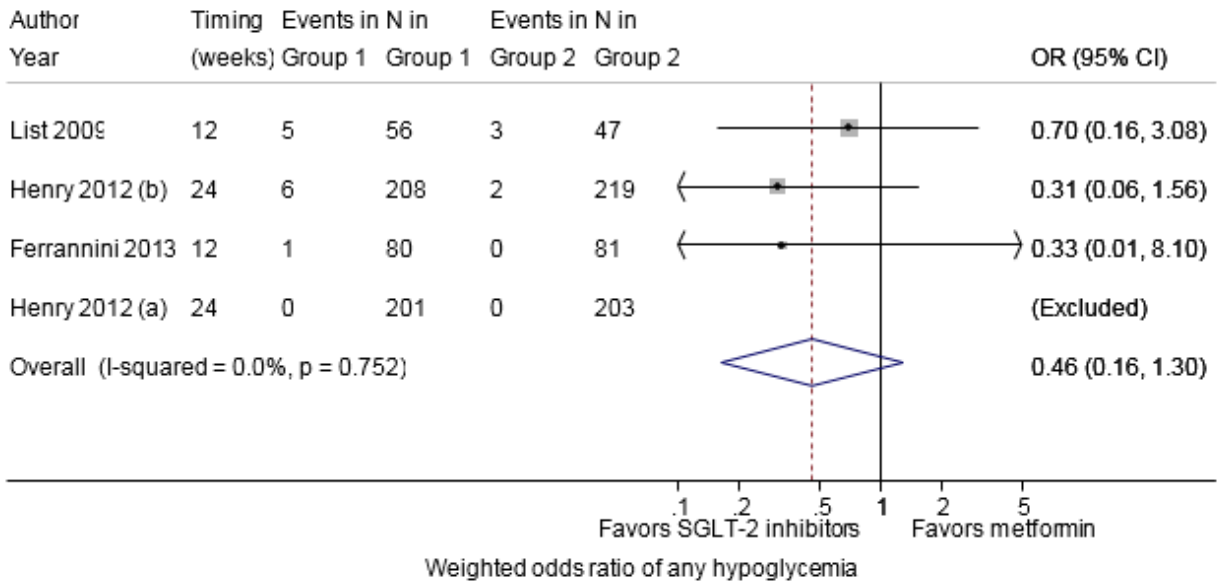
Metformin Versus SGLT-2 Inhibitors

Four RCTs (reported in three articles) compared metformin with SGLT-2 inhibitors and reported on total hypoglycemia.[88, 89, 239] The meta-analysis favored SGLT-2 inhibitors versus metformin for any hypoglycemia, although the combined result was not statistically significant (Figure 56).

In a 2013 RCT, Ferrannini et al.,[90] an extension of one of the included studies[239] with 78 weeks of followup found slightly higher rates of hypoglycemia in the metformin arm (3.6%) versus empagliflozin arms (10 mg, 0.9%; 25 mg, 1.8%); we did not include this study in the meta-analysis because of its longer duration.

Two studies reported no events of severe hypoglycemia.[88] (SOE: Moderate; SGLT-2 inhibitors favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Figure 56. Pooled odds ratio of any hypoglycemia comparing metformin with SGLT-2 inhibitors



CI = confidence interval; Group 1 = metformin; Group 2 = sodium-glucose co-transporter-2; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

Metformin Versus GLP-1 Receptor Agonists

Two of three RCTs compared metformin with GLP-1 receptor agonists (duration 26 to 52 weeks) and found a slightly higher risk of mild or moderate hypoglycemia for GLP-1 receptor agonists compared to metformin (Table 59).[73, 91, 92] The third RCT reported similar risks across arms for this outcome. No study reported severe hypoglycemia events in either arm. (SOE: Low; Metformin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 59. Randomized controlled trials comparing metformin with GLP-1 receptor agonists on hypoglycemia

Author, Year	Followup (Weeks)	Metformin (Dose*)	GLP-1 Receptor Agonist (Dose*)	Definition of Hypoglycemia	Results† (Metformin Vs GLP-1 Receptor Agonist)
Russell-Jones, 2012[73]	26	Metformin (max 2500 mg)	Exenatide (fixed at 2.0 mg weekly)	Mild-moderate (signs or symptoms associated with BG < 3.0 mmol/L (either self-treated or resolved independently))	0/246 (0%) vs 5/248 (2.0%)
				Severe‡	0/246 (0%) vs 0/248 (0%)
				Total (signs or symptoms)	10/246 (4.1%) vs 13/248 (5.2%)
Umpierrez, 2014[91]	52	Metformin (max 2000 mg or ≥ 1500 mg depending on tolerability)	Dulaglutide (fixed at 0.75 mg weekly)	Total (signs or symptoms and/or PG ≤ 70 mg/dL [3.9 mmol/L])	34/268 (12.7%) vs 30/270 (11.1%)
				Severe (required third party assistance)	0/268 (0%) vs 0/270 (0%)
Umpierrez, 2014[91]	52	Metformin (max 2000 mg or ≥ 1500 mg depending on tolerability)	Dulaglutide (fixed at 1.5 mg weekly)	Total (signs or symptoms and/or PG ≤ 70 mg/dL [3.9 mmol/L])	34/268 (12.7%) vs 33/269 (12.3%)
				Severe (required third party assistance)	0/268 (0%) vs 0/269 (0%)
Yuan, 2012[92]	26	Metformin (max 2000 mg)	Exenatide (max 2.0 mg)	Mild (not specified)	1/26 (3.8%) vs 4/33 (12.1%)
				Severe (required third party assistance or hospital treatment)	0/26 (0%) vs 0/33 (0%)

BG = blood glucose; GLP-1 = glucagon-like peptide-1; max = maximum; mg = milligrams; mg/dL = milligram per deciliter; mmol/L = millimole per liter; PG = plasma glucose

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

‡ Severe hypoglycemia was defined as symptoms resulting in loss of consciousness or seizure that showed prompt recovery after glucose administration, or documented blood glucose less than 3.0 mmol/L that required the assistance of another person because of severe impairment in consciousness.

Thiazolidinediones Versus Sulfonylureas

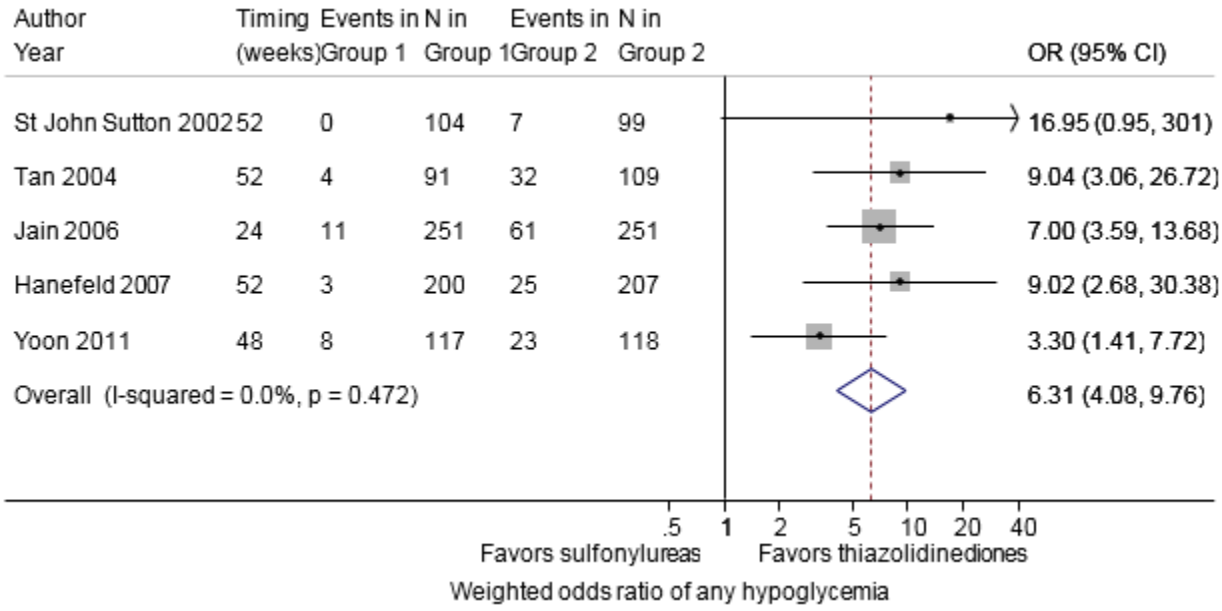
Nine RCTs compared thiazolidinedione with sulfonylurea monotherapy and reported on hypoglycemia (Table 60).[50, 60, 74, 94, 95, 100, 103, 217, 253]

Results from the meta-analysis of five sufficiently-homogeneous, short-term RCTs showed that the risk of total hypoglycemia was higher for sulfonylurea compared with thiazolidinedione monotherapy (pooled OR for sulfonylurea compared with thiazolidinedione monotherapy, 6.31; 95% CI, 4.08 to 9.76) (Figure 57). We did not find evidence of significant statistical heterogeneity, and removal of any one study did not change the overall inference.

We did not include one short-term (16 weeks) study in the meta-analysis, because it reported on the number of events and not the number of participants experiencing events; this study reported two events of hypoglycemia in the thiazolidinedione arm and three events in the sulfonylurea arm.[253] We excluded another short-term (24 weeks) RCT from the meta-analysis, because its mean daily dose of glimepiride (1.5 mg/day) was much lower than the dosing of sulfonylureas in the other studies included in the meta-analysis. This study still found higher rates of hypoglycemia (blood glucose < 60 mg/dL) in the sulfonylurea (7/95, 7.4%) than thiazolidinedione (5/96, 5.2%) arm.[103]

The longer study, ADOPT, also found higher rates of total hypoglycemia for the sulfonylurea arm (557/1441, 38.7%) compared with the thiazolidinedione arm (142/1456, 9.8%). This study also found more severe hypoglycemia in the sulfonylurea arm (8/1441, 0.6%) compared with the thiazolidinedione arm (1/1456, 0.1%). One of the short-term studies reported that two participants experienced severe hypoglycemia in the sulfonylurea arm but did not report on this outcome for the thiazolidinedione arm.[94] (SOE: High; Thiazolidinediones favored for mild, moderate, or total hypoglycemia) (SOE: Moderate; Thiazolidinediones favored for severe hypoglycemia)

Figure 57. Pooled odds ratio of any hypoglycemia comparing thiazolidinediones with sulfonylureas



CI = confidence interval; Group 1 = thiazolidinediones; Group 2 = sulfonylureas; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Table 60. Randomized controlled trials comparing thiazolidinediones with sulfonylureas on mild to moderate hypoglycemia

Author, Year Study Design	Followup (Weeks)	TZD (Dose*)	SU (Dose*)	Definition of Hypoglycemia	Results† (TZD Vs SU)
Jain‡, 2006[95]	24	Pioglitazone (max 45 mg)	Glyburide (max 15 mg)	2 or more symptoms or BG < 60 mg/dL	11/251 (4%) vs 61/251 (24%)
St. John Sutton‡, 2002[217]	52	Rosiglitazone (max 8 mg)	Glyburide (max 20 mg)	Symptomatic	0/104 (0%) vs 7/99 (7%)
Tan‡, 2004[100]	52	Pioglitazone (max 45 mg)	Glibenclamide (max 10.5 mg)	Symptoms or BG < 50 mg/dL	4/91 (4%) vs 32/109 (29%)
Hanefeld‡, 2007[94]	52	Rosiglitazone (max 8 mg)	Glibenclamide (max 15 mg)	Not reported	3/200 (2%) vs 25/207 (12%)
Kahn, 2006[50]	312	Rosiglitazone (max 8 mg)	Glyburide (max 15 mg)	Self-reported	142/1456 (10%) vs 557/1441 (39%)
Yamanouchi, 2005[60]	12	Pioglitazone (30 mg for women and 45 mg for men)	Glimepiride (max 2 mg)	Not reported	0/38 (0%) vs 1/37 (3%)
Agarwal, 2005[253]	16	Pioglitazone	Glipizide	Not reported	2 events among 22 patients vs 3 events among 22 patients
Shihara, 2011[103]	24	Pioglitazone (mean 23.24 mg; max 30 mg for women and 45 mg for men)	Glimepiride (mean 1.51 mg; max 6 mg)	BG < 60 mg/dL	5/96 (5%) vs 6/95 (6%)
Yoon‡, 2011[74]	48	Rosiglitazone (mean 5.9 mg; max 8 mg)	Glimepiride (mean 4.5 mg; max 8 mg)	Symptomatic	8/117 (7%) vs 23/118 (19%)

BG = blood glucose; mg = milligrams; mg/dL = milligrams per deciliter; SU = sulfonylurea; TZD = thiazolidinedione

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

‡ Included in meta-analysis.

Thiazolidinediones Versus DPP-4 Inhibitors

Three short-term studies evaluated hypoglycemia for the comparison of thiazolidinediones to DPP-4 inhibitors (Table 61).[48, 73, 104] Of two studies reporting on total hypoglycemia, rates were similar in one study and higher in the pioglitazone versus the sitagliptin arm in the other.[48, 73] Two studies reported on severe hypoglycemia and observed no events.[73, 104] (SOE: Insufficient for total hypoglycemia; Low: Neither favored for severe hypoglycemia)

Table 61. Randomized controlled trials comparing thiazolidinediones with DPP-4 inhibitors on hypoglycemia

Author, Year	Followup (Weeks)	TZD (Dose*)	DPP-4 Inhibitor (Dose*)	Definition of Hypoglycemia	Results† (TZD Vs DPP-4 Inhibitor)
Alba, 2013[48]	12	Pioglitazone (fixed at 30 mg)	Sitagliptin (fixed at 100 mg)	Total (all reports of hypoglycemia; no glucose measurement required)	2/54 (3.7%) vs 0/52 (0%)
Rosenstock, 2010[104]	26	Pioglitazone (fixed at 30mg)	Alogliptin (fixed at 25 mg)	Severe (required third party assistance)	0/163 (0%) vs 0/164 (0%)
Russell-Jones, 2012[73]	26	Pioglitazone (max 45 mg)	Sitagliptin (fixed at 100 mg)	Total (signs or symptoms) Severe‡	6/163 (3.7%) vs 5/163 (3.1%) 0/163 (0%) vs 0/163 (0%)

DPP-4 = dipeptidyl peptidase-4; mg = milligrams; TZD = thiazolidinedione

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

‡ Severe hypoglycemia was defined as symptoms resulting in loss of consciousness or seizure that showed prompt recovery after glucose administration, or documented blood glucose less than 3.0 mmol/L that required the assistance of another person because of severe impairment in consciousness.

Thiazolidinediones Versus GLP-1 Receptor Agonists

Two RCTs (26 and 48 weeks in duration) found higher rates of non-severe hypoglycemia for exenatide compared to pioglitazone but no difference in severe hypoglycemia (no events) across arms.[73, 105] In the 26-week trial 0/163 (0%) experienced mild hypoglycemia in the pioglitazone arm versus 5/248 (2%) in the exenatide arm.[73] In the 48-week trial, corresponding event (symptoms with blood glucose <3.9 mmol/l [<70 mg/dl]) rates were 13/142 (9.2%) and 5/136 (3.7%) in the exenatide and pioglitazone arms, respectively.[105] (SOE: Low; Thiazolidinediones favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Sulfonylureas Versus DPP-4 Inhibitors

Comparisons for both mild and severe hypoglycemia favored the DPP-4 inhibitor arms over sulfonylureas (for mild, moderate, or total hypoglycemia for SU vs. DPP-4 inhibitors: range in OR 3.8 to 12.4; range in RD 6% to 15%). Four RCTs examined hypoglycemia with this comparison; differences in followup length and definitions of hypoglycemia precluded a meta-analysis (Table 62). (SOE: Moderate; DPP-4 inhibitors favored for mild, moderate, or total hypoglycemia) (SOE: Low; DPP-4 inhibitors favored for severe hypoglycemia)

Table 62. Randomized controlled trials comparing sulfonylureas with DPP-4 inhibitors on hypoglycemia

Author, Year	Followup (Weeks)	SU (Dose*)	DPP-4 Inhibitor (Dose*)	Definition of Hypoglycemia	Results† (SU Vs DPP-4 Inhibitor)
Arjona Ferreira, 2013[107]	58	Glipizide (max 20 mg; mean 7.7 mg)	Sitagliptin (fixed at 50 mg for those with moderate renal insufficiency and 25 mg for those with severe renal insufficiency)	Severe (required third party assistance or medical intervention or exhibited markedly depressed level of consciousness, loss of consciousness, or seizure) Total (signs and/or symptoms)	6/212 (2.8%) vs 3/210 (1.4%) 36/212 (17%) vs 13/210 (6.2%); *P* < 0.001
Gupta, 2013[260]	24	Glimepiride (max 4 mg)	Sitagliptin (max 200 mg)	Total (not specified)	11 episodes among 71 patients vs 3 episodes among 77 patients
Barnett, 2012[106]	34	Glimepiride (max 4 mg)	Linagliptin (fixed at 5 mg)	Mild-moderate (Symptoms and/or PG ≤ 70 mg/dL [3.9 mmol/]) Severe (required third party assistance)	5/64 (7.8%) vs 3/137 (2.2%) 0/64 (0%) vs 0/137 (0%)
Scott, 2007[108]	12	Glipizide (max 20 mg)	Sitagliptin (fixed at 25 mg)	Total (self-report and glucose measurements)	21/123 (17.1%) vs 5/123 (4.1%)
Scott, 2007[108]	12	Glipizide (max 20 mg)	Sitagliptin (fixed at 50 mg)	Total (self-report and glucose measurements)	21/123 (17.1%) vs 5/123 (4.1%)
Scott, 2007[108]	12	Glipizide (max 20 mg)	Sitagliptin (fixed at 100 mg)	Total (self-report and glucose measurements)	21/123 (17.1%) vs 2/122 (1.6%)

DPP-4 = dipeptidyl peptidase-4; max = maximum; mg = milligrams; mg/dL = milligrams per deciliter; mmol/L = millimole per liter; PG = plasma glucose; SU = sulfonylurea

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

Sulfonylureas Versus GLP-1 Receptor Agonists

Sulfonylureas had greater risk of mild to moderate hypoglycemia compared with GLP-1 receptor agonists (range in OR 3.1 to 5.3; range in RD 12% to 21%) (Table 63). Five studies assessed this outcome and could not be pooled because of heterogeneity in outcome definitions and followup length. No study reported any events of severe hypoglycemia. (SOE: Moderate; GLP-1 receptor agonists favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 63. Randomized controlled trials comparing sulfonylureas with GLP-1 receptor agonists on hypoglycemia

Author, Year	Followup (Weeks)	SU (Dose*)	GLP-1 Receptor Agonist (Dose*)	Definition of Hypoglycemia	Results† (SU Vs GLP-1 Receptor Agonist)
Garber, 2011[113]	104	Glimepiride (max 8mg)	Liraglutide (max 1.2 mg)	Mild-moderate (did not require assistance, BG < 56 mg/dL [3.1 mmol/L])	64/248 (25.8%) vs 30/251 (12%)
				Severe (required third-party assistance)	0/248 (0%) vs 0/251 (0%)
Garber, 2011[113]	104	Glimepiride (max 8 mg)	Liraglutide (max 1.8 mg)	Mild-moderate (did not require assistance, BG < 56 mg/dL [3.1 mmol/L])	64/248 (25.8%) vs 25/247 (10.1%)
				Severe (required third-party assistance)	0/248 (0%) vs 1/247 (0.4%)‡
Kaku, 2011[110]	52	Glibenclamide (fixed at 1.25 -2.5 mg)	Liraglutide (max 0.9 mg)	Mild-moderate (self-treated)	1.10 events per patient-year vs 0.19 events per patient-year
				Severe (required third party assistance)	0/132 (0%) vs 0/268 (0%)
Madsbad, 2004[111]	12	Glimepiride (max 4 mg)	Liraglutide (Fixed (0.60 mg))	Mild-moderate (BG < 2.8 mmol/L)	4/26 (15.4%) vs 1/30 (3.3%)
Madsbad, 2004[111]	12	Glimepiride (max 4 mg)	Liraglutide (Fixed (0.75 mg))	Mild-moderate (BG < 2.8 mmol/L)	4/26 (15.4%) vs 0/28 (0%)
Seino, 2010[109]	24	Glibenclamide (max 2.5 mg)	Liraglutide (max 0.9 mg)	Mild-moderate (symptoms)	45/132 (34.1%) vs 36/268 (13.4%)
				Mild-moderate (symptoms and BG < 3.1 mmol/L)	29/132 (22%) vs 22/268 (8.2%)
				Severe (required third party assistance)	0/132 (0%) vs 0/268 (0%)

BG = blood glucose; GLP-1 = glucagon-like peptide-1; max = maximum; mg = milligrams; mg/dL = milligrams per deciliter; mmol/L = millimole per liter; SU = sulfonylurea

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

‡ Event in the context of insulin infusion as part of a "sub-study" procedure.

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

One study assessed hypoglycemia for the comparison of DPP-4 inhibitors versus SGLT-2 inhibitors.[114] The study compared sitagliptin with empagliflozin at 24 weeks, with one of 223 patients (<1%) in the sitagliptin arm with any hypoglycemia, one of 224 patients (<1%) in the 10 mg empagliflozin arm, and one of 223 patients (<1%) in the 25 mg empagliflozin arm. No

patients experienced severe hypoglycemia. (SOE: Low; Neither favored for mild, moderate, or total hypoglycemia)

DPP-4 Inhibitors Versus GLP-1 Receptor Agonists

One 26-week RCT assessed hypoglycemia for the comparison of DPP-4 inhibitors versus GLP-1 receptor agonists.[73] Investigators compared sitagliptin with exenatide at 26 weeks. Total hypoglycemia was slightly higher for the GLP-1 receptor agonist arm: 13/248 (5.2%) patients in the exenatide arm vs. 5/163 (3.1%) in the sitagliptin arm. Mild hypoglycemia was also higher in the exenatide (5/248, 2.0%) than the sitagliptin arm (0/163, 0%). No patients had severe hypoglycemia in either arm. (SOE: Low; DPP-4 inhibitors favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

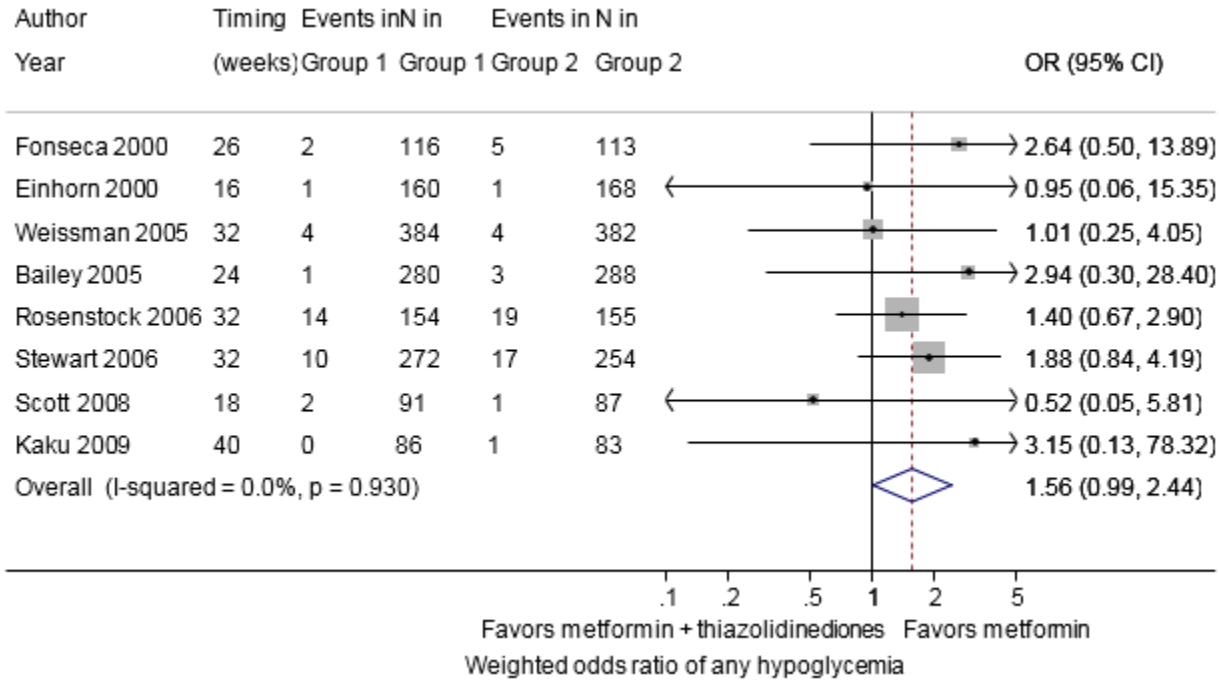
Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

More patients experienced hypoglycemia in the combination arm than in the metformin-alone arm. We combined eight sufficiently-homogeneous, short-term RCTs and found an increased odds of mild or moderate hypoglycemia for metformin plus thiazolidinedione versus metformin alone (pooled OR, 1.56; 95% CI, 0.99 to 2.44) (Figure 58).[59, 117-120, 122, 123, 247] We did not find statistical heterogeneity.

We excluded one RCT from this meta-analysis because its longer followup. This study compared metformin (titrated to a maximum of 2000 mg daily) with metformin plus rosiglitazone (titrated to a maximum of 8 mg/2000 mg daily) at 80 weeks and reported 10 total hypoglycemia events in the metformin-alone arm (3% of patients), and 20 hypoglycemia events in the metformin-rosiglitazone arm (6% of patients).[127] These results were consistent with our findings reported above. Another study was excluded from the meta-analysis because of its low-dose combination arm. The study compared metformin (fixed at 1700 mg daily) with a lower-dose combination arm [metformin (fixed at 500 mg daily) and rosiglitazone (fixed at 4 mg daily)] and reported no hypoglycemia in either arm at 24 weeks.[124] (SOE: High, Metformin favored for mild, moderate, or total hypoglycemia)

Figure 58. Pooled odds ratio of any hypoglycemia comparing metformin with combination of metformin plus a thiazolidinedione

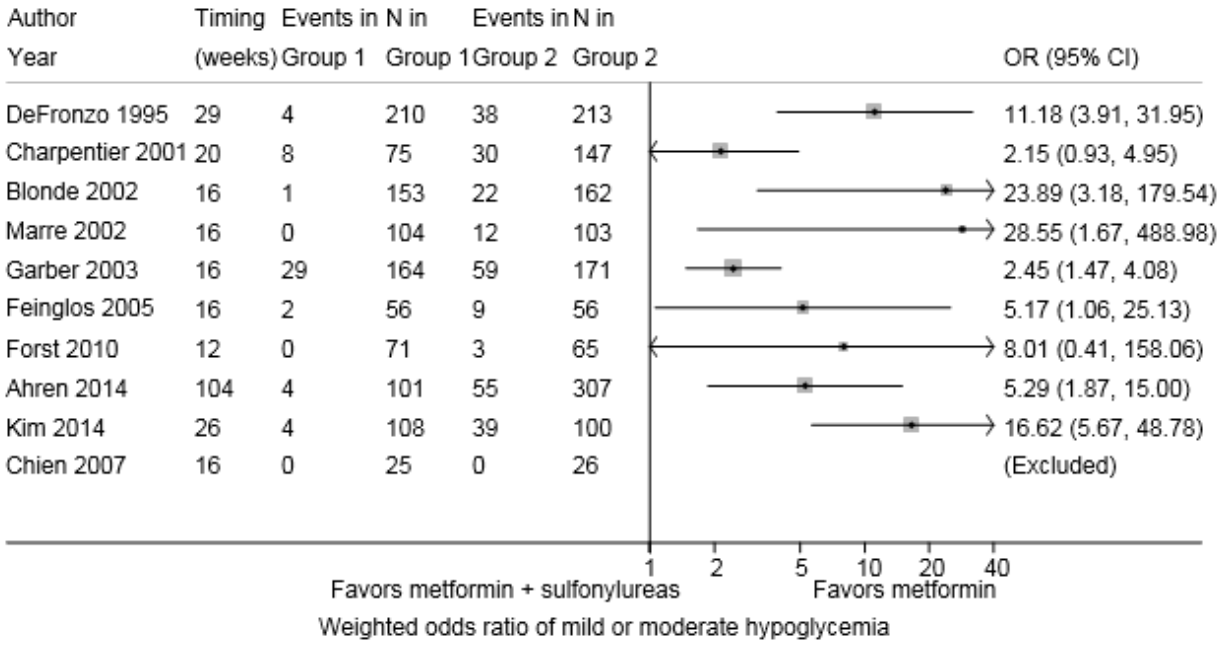


CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus thiazolidinedione; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

Ten RCTs compared metformin with the combination of metformin plus a sulfonylurea and found more mild, moderate, and total hypoglycemia in the combination arms compared with monotherapy arms.[128, 129, 131, 132, 136-141] We did not pool these studies because of differences in definitions of hypoglycemia and dosing of medications; individual study characteristics are shown in Figure 59 and Table 64. Rates of hypoglycemia did not appear higher with glyburide than with any other sulfonylurea. Only two studies reported on severe hypoglycemia and did not report any events.[140, 141] (SOE: Moderate; Metformin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Figure 59. Odds ratios for studies evaluating mild or moderate hypoglycemia comparing metformin with combination of metformin plus a sulfonylurea



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus sulfonylurea; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Table 64. Additional randomized controlled trials comparing metformin with a combination of metformin plus a sulfonylurea on hypoglycemia

Author, Year	Followup (Weeks)	Metformin (Dose in mg*)	Metformin + SU (Dose*)	Definition of Hypoglycemia	Results† (Metformin Vs SU)
Ahren, 2014[141]	104	Metformin (fixed at ≥ 1500)	Metformin (fixed at ≥ 1500) + glimepiride (max 4)	Mild-moderate (Asymptomatic, but BG ≤ 3.9 mmol/L) Mild-moderate (Symptomatic and BG ≤ 3.9 mmol/L) Severe (required third party assistance)	1/101 (1.0%) vs 3/307 (1.0%) 4/101 (4.0%) vs 55/307 (17.9%) 0/101 (0%) vs 0/307 (0%)
Kim, 2014[140]	26	Metformin (max 2500)	Metformin (max 2000) + glimepiride (fixed at 1-8)	Total (symptomatic) Severe (not specified)	4/108 (3.7%) vs 39/100 (0.4%) 0/108 (0%) vs 0/100 (0%)
Forst, 2010[139]	12	Metformin (fixed)	Metformin (fixed) + glimepiride (max 3)	Total (not specified)	0/71 (0%) vs 3/65 (4.6%)
DeFronzo, 1995[137]	29	Metformin (max 2500)	Metformin (max 2500) + glyburide (max 20)	Not reported	4/210 (2%) vs 38/213 (18%)
Charpentier, 2001[136]	20	Metformin (fixed at 2550)	Metformin (fixed at 2550) + glimepiride (max 6)	Symptomatic	8/75 (11%) vs 30/147 (20%)
Marre, 2002[132]	16	Metformin (max 2000)	Metformin (max 2000) + glibenclamide (max 10)	Symptoms or labs	0/104 (0%) vs 12/103 (12%)
Blonde, 2002[131]	16	Metformin (max 2000)	Metformin (max 2000) + glyburide (max 20)	FSG<=60mg/dl + symptomatic	1/153 (1%) vs 22/162 (14%)
Garber, 2003[129]	16	Metformin (max 2000)	Metformin (max 1000 mg) + glyburide (max 5)	Symptoms suggesting hypoglycemia	29/164 (18%) vs 59/171 (35%)
Feinglos, 2005[128]	16	Metformin (fixed at ≥ 1000)	Metformin (fixed at ≥ 1000 mg) + glipizide (fixed at 2.5)	FSG <60 mg/dl with symptoms or FSG <50 mg/dl without symptoms or FBG<55 mg/dl without symptoms	2/56 (4%) vs 9/56 (16%)
Chien, 2007[138]	16	Metformin (max 2000)	Metformin (max 2000 mg) + glyburide (max 20)	Symptomatic or BG < 60 mg/dL	0/25 (0%) vs. 0/26 (0%)

BG = blood glucose; FBG = fasting blood glucose; FSG = fingerstick glucose; max = maximum; mg = milligrams; mmol/L = millimole per liter; SU = sulfonylurea

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

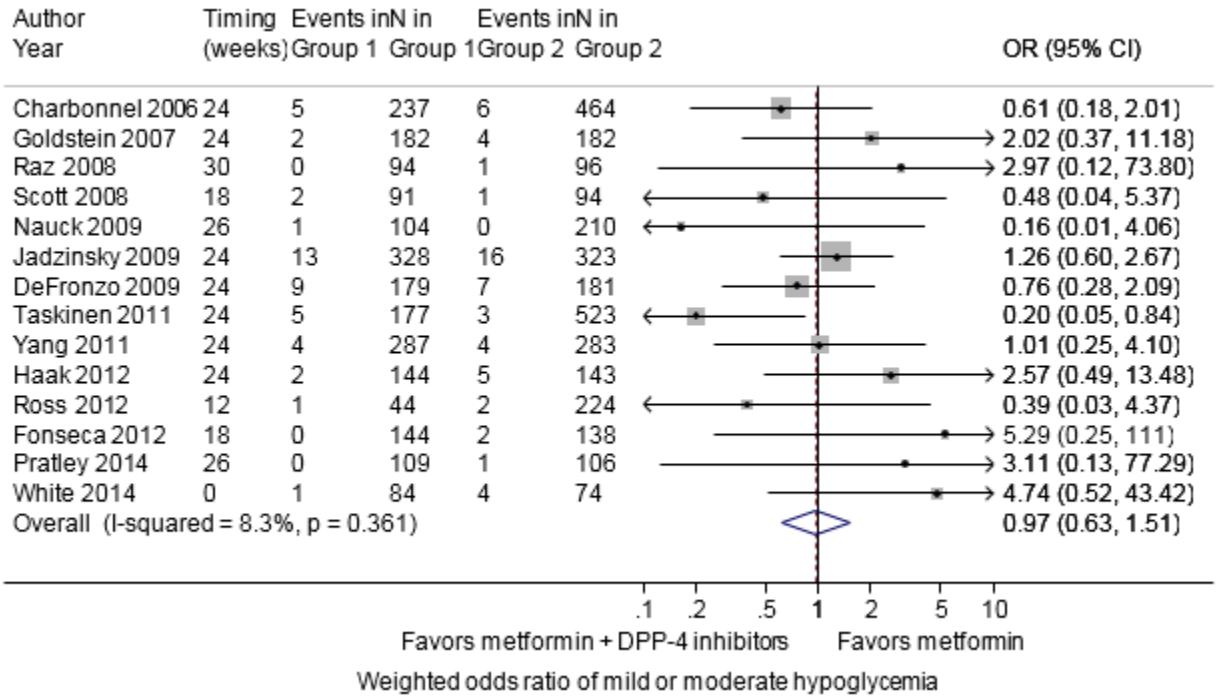
We included 27 studies (31 publications) for the comparison of metformin and combination of metformin plus a DPP-4 inhibitor for hypoglycemia.[51, 80, 81, 83-87, 118, 139, 141-156, 159-162, 164, 261] Six RCTs were from the 2010 report,[80, 81, 83, 142-144, 261] with two RCTs being published extensions of those prior studies.[85, 87] We identified 21 new studies for this report. Overall, mild, moderate, total, or severe hypoglycemia were similar for metformin versus the combination of metformin plus a DPP-4 inhibitor.

Mild or Moderate Hypoglycemia

One long-term RCT reported mild hypoglycemia in 1% of patients in the metformin arm compared with 1.3% of patients in the metformin plus sitagliptin arm at 104 weeks.[141] Fourteen short-term studies reported on mild or moderate hypoglycemia (Figure 60).[80, 83, 84, 86, 118, 142-144, 147, 148, 151, 152, 155, 261] The pooled odds ratio for mild or moderate hypoglycemia across these studies suggested similar risk of hypoglycemia for the combination of metformin plus a DPP-4 inhibitor compared to metformin (pooled OR, 0.97; 95% CI, 0.63 to 1.51). We did not identify significant statistical heterogeneity, and removal of any single study did not affect the overall inference of no difference in hypoglycemia risk across treatments.

Another short-term RCT reported mild hypoglycemia events per person year and found a higher rate of events (4.8 events per person-year) in the metformin arm compared with the metformin plus sitagliptin arm (0.1 events per person-year) at 26 weeks.[159]

Figure 60. Pooled odds ratio of mild or moderate hypoglycemia comparing metformin with combination of metformin plus a DPP-4 inhibitor



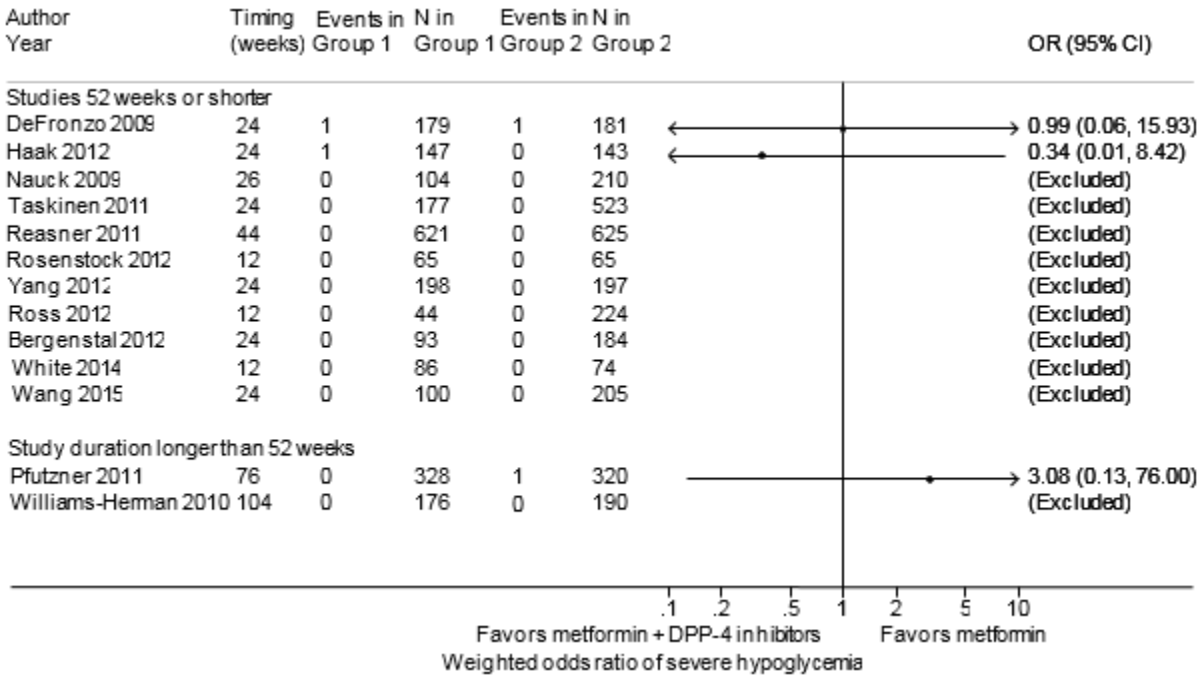
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Severe Hypoglycemia

Thirteen RCTs reported on severe hypoglycemia for this comparison.[51, 86, 144, 145, 148, 151, 152, 155, 156, 160, 261] Few events of severe hypoglycemia were reported with 10 of 13 studies reporting no events (Figure 61).

Figure 61. Pooled odds ratio of severe hypoglycemia comparing metformin with combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

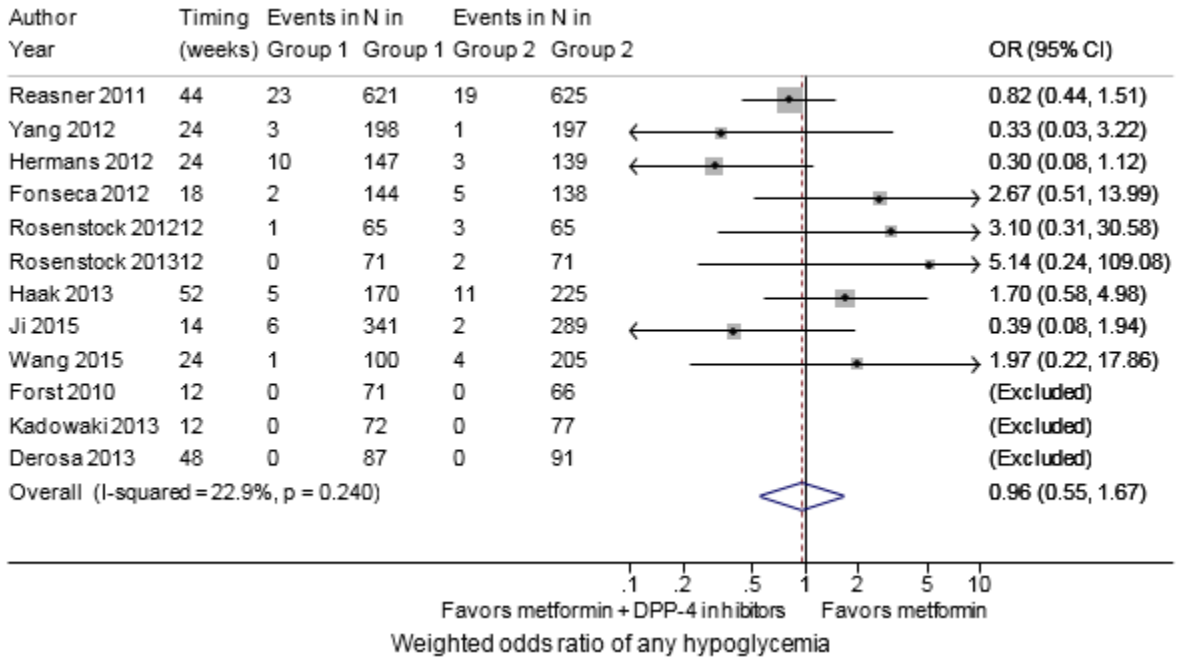
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Total Hypoglycemia

Eleven studies reported on total hypoglycemia events with short term (<52 week) followup.[139, 145, 147-150, 153, 156, 160-162, 164] The pooled odds ratio for metformin vs. metformin plus a DPP-4 inhibitor was 0.96 (95% CI, 0.55, 1.67), suggesting similar risk of total hypoglycemia for metformin and the combination of metformin plus a DPP-4 inhibitor (Figure 62). We did not find evidence of significant statistical heterogeneity, and the exclusion of a single study did not change the inference. Three studies shown in Figure 62 did not contribute to the pooled OR because no events occurred in either arm.[139, 149, 150]

One study had longer follow up (76 weeks) and reported 20 events in the metformin arm (6.1%) compared with 15 in the metformin plus saxagliptin arm (4.7%) at 76 weeks.[87] (SOE: High; Neither favored for mild, moderate, or total hypoglycemia) (SOE: Moderate; Neither favored for severe hypoglycemia)

Figure 62. Pooled odds ratio of any hypoglycemia comparing metformin with combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

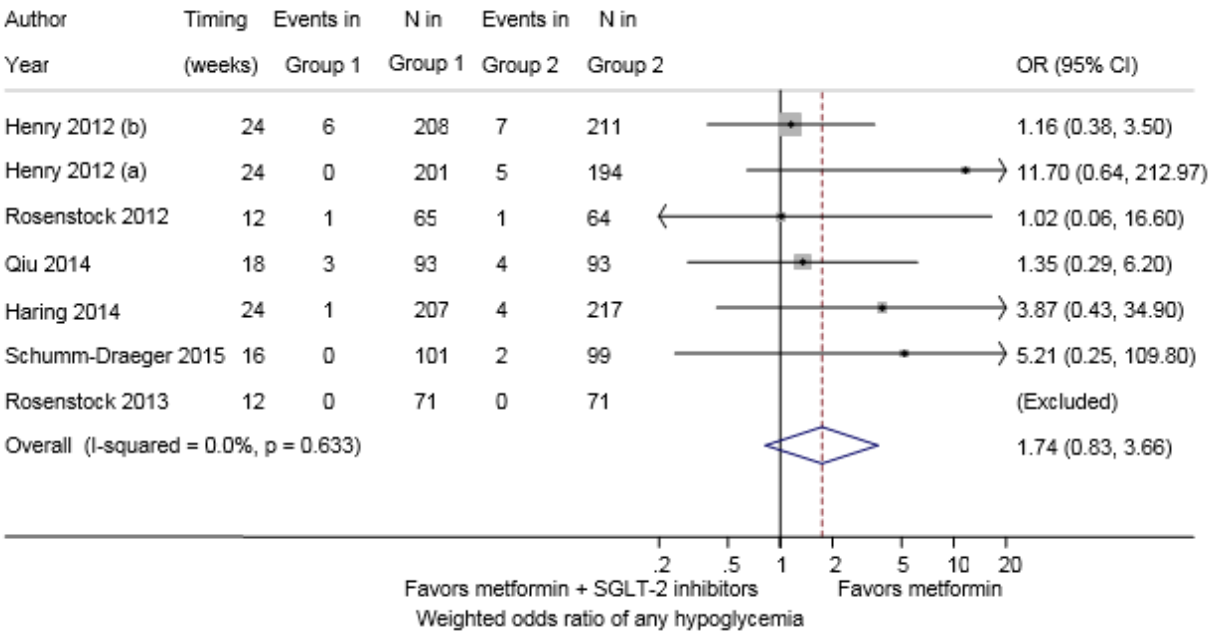
Seven short-term studies (published in six articles) reported on total hypoglycemia.[88, 153, 156, 165, 166, 168] Meta-analysis of these studies demonstrated a weighted pooled odds ratio for metformin plus an SGLT-2 inhibitor vs. metformin of 1.74 (95% CI, 0.83, 3.66), suggesting a possible increased risk of total hypoglycemia for the combination treatment (Figure 63).

Another study reported on total hypoglycemia with 78 weeks of followup and reported higher rates of total hypoglycemia in the metformin compared to metformin plus SGLT-2 inhibitor arm: two patients of 56 in the metformin arm (3.6%), three patients of 166 (1.8%) in the arm receiving 10 mg of empagliflozin, and four patients of 166 (2.4%) in the arm receiving 25 mg of empagliflozin.[90] Mean metformin dose was not reported in this study, and the article states that participants were on their pre-enrollment dose of metformin (1500 mg or greater or maximum tolerated dose) during the study.[90]

One long-term RCT (102 weeks) study reported on mild hypoglycemia events and reported four events in both the metformin arm (4.4%) and the metformin plus dapagliflozin combination arm (4.4%).[169]

Six short-term studies (published in five articles) reported on severe hypoglycemia events with followup of less than 1 year (range 12 to 24 weeks), and none of these studies reported any severe events.[88, 156, 165, 166, 168] One study with more 102 weeks of followup reported no severe hypoglycemic events.[170] (SOE: Moderate; Metformin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Figure 63. Pooled odds ratio of any hypoglycemia comparing metformin with combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

Metformin Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Four studies compared metformin with a combination of metformin plus a GLP-1 receptor agonist,[141, 159, 171, 174] and reported on hypoglycemia (Table 65). The single long-term (104-week) study showed no severe hypoglycemia in either arm and did not find a clinically-significant difference in mild-moderate hypoglycemia between arms; this study had large losses to followup and did not use an intention-to-treat approach to analysis.[141]

Two of three shorter studies (26 to 48 weeks) showed no difference in non-severe hypoglycemia for the metformin and combination arms, but definitions of hypoglycemia varied across these three studies.[159, 171, 174] The study suggesting an increased risk of hypoglycemia in the metformin plus GLP-1 receptor agonist arms versus metformin had large losses to followup across its arms. No severe hypoglycemia events were reported in this study, which was the only short-term study reporting on this outcome.[159] (SOE: Low; Neither favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 65. Randomized controlled trials comparing metformin with a combination of metformin plus a GLP-1 receptor agonist on hypoglycemia

Author, Year	Followup (Weeks)	Metformin (Dose*)	Metformin + GLP-1 Receptor Agonist (Dose*)	Definition of Hypoglycemia	Results† (Metformin Vs Metformin + GLP-1 Receptor Agonist)
Ahren, 2014[141]	104	Metformin (fixed at ≥ 1500 mg)	Metformin (fixed at ≥ 1500 mg) + albiglutide (max 50 mg weekly)	Mild-moderate (Asymptomatic, but PG ≤ 3.9 mmol/L) Mild-moderate (Symptomatic and PG ≤ 3.9 mmol/L) Severe (required third party assistance)	1/101 (1%) vs 4/302 (1.3%) 4/101 (4.0%) vs 9/302 (3.0%) 0/101 (0%) vs 0/302 (0%)
Nauck, 2014[159]	26	Metformin (fixed at ≥ 1500 mg)	Metformin (fixed at ≥ 1500 mg) + dulaglutide (fixed at 0.75 mg/week)	Mild-moderate (Signs and symptoms and/or PG ≤ 70 mg/dL [3.9 mmol/L]) Severe (required third party assistance)	2/177 (1.1%)‡ vs 16/302 (5.3%) 0/177 (0%)‡ vs 0/302 (0%)
Nauck, 2014[159]	26	Metformin (fixed at ≥ 1500 mg)	Metformin (fixed at ≥ 1500 mg) + dulaglutide (fixed at 1.5 mg/week)	Mild-moderate (Signs and symptoms and/or PG ≤ 70 mg/dL [3.9 mmol/L]) Severe (required third party assistance)	2/177 (1.1%)‡ vs 31/304 (10.2%) 0/177 (0%)‡ vs 0/304 (0%)
Derosa, 2013[171]	48	Metformin (mean 2500 mg)	Metformin (mean 2500 mg) + exenatide (max 20 mcg)	Total (FPG < 60 mg/dL)	0/85 (0%) vs 0/86 (0%)
DeFronzo, 2005[174]	30	Metformin (fixed at ≥ 1500 mg)	Metformin (fixed at ≥ 1500 mg) + exenatide 10 mcg	Symptoms (with or without PG <60 mg/dl [3.3 mmol/l])	6/113 (5.3%) vs. 5/110 (4.5%)
DeFronzo, 2005[174]	30	Metformin (fixed at ≥ 1500 mg)	Metformin (fixed at ≥ 1500 mg) + exenatide 20 mcg	Symptoms (with or without PG <3.3 mmol/l)	6/113 (5.3%) vs. 6/110 (5.3%)

FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; mcg = micrograms; mg = milligrams; mg/dL = milligrams per deciliter; mmol/L = millimole per liter; PG = plasma glucose; vs = versus

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

‡ Although study had 52 weeks of followup, incidence of hypoglycemia was only available at 26 weeks. In the trial, patients were switched from a combination of metformin and placebo to a combination of metformin and sitagliptin.

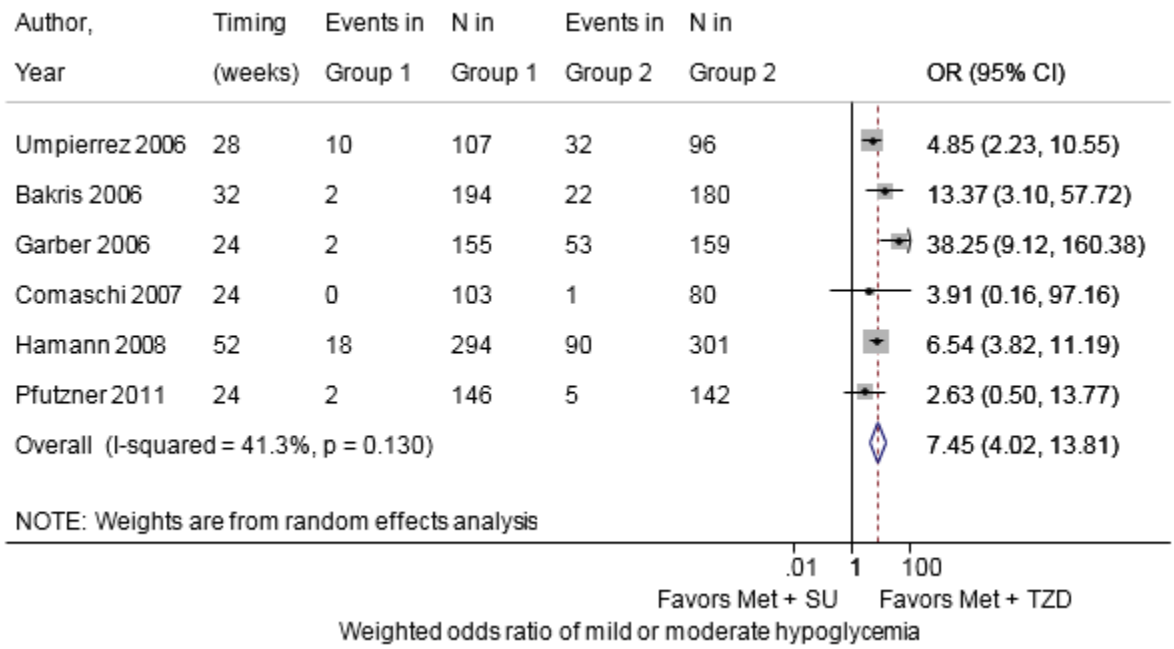
Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Six short-duration RCTs reporting on mild or moderate hypoglycemia compared the combination of metformin plus a thiazolidinedione with metformin plus a sulfonylurea, showing higher risk of hypoglycemia in the metformin plus sulfonylurea arm (pooled OR, 7.5; 95% CI, 4.0 to 13.8) (Figure 64).[175, 177, 178, 180, 183, 185] The trial by Hamann et al. was designed so that patients were withdrawn from the study if they did not reach an efficacy target after 8 weeks of treatment.[175] The rates of hypoglycemia were high as medications were titrated up to efficacy, although the relative odds of hypoglycemia in the two arms were comparable to the other studies. No single study strongly influenced the results of the meta-analysis, and no substantial heterogeneity was identified.

One study reported on severe hypoglycemia, showing results consistent with the mild to moderate hypoglycemia outcome.[180] In Garber et al., seven of 159 patients had severe hypoglycemic events in the metformin plus sulfonylurea arm, and none did in the metformin plus thiazolidinedione arm.[180] This study included patients with high baseline HbA1c and had a higher proportion of Asian patients than most studies (12% Asian). (SOE: High; Combination of metformin plus a thiazolidinedione favored for mild, moderate, or total hypoglycemia) (SOE: Low; Combination of metformin plus a thiazolidinedione favored for severe hypoglycemia)

Figure 64. Pooled odds ratio of any hypoglycemia comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea



CI = confidence interval; Group 1 = combination of metformin plus thiazolidinedione; Group 2 = combination of metformin plus a sulfonylurea; Met = metformin; OR = odds ratio; SU = sulfonylurea; TZD = thiazolidinedione
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Three studies (two RCTs and one observational study) compared the combination of metformin plus a thiazolidinedione with metformin plus a DPP-4 inhibitor, showing no clear differences between-groups in hypoglycemia risk.[186, 188, 262] One low-quality study randomized 56 patients to metformin and rosiglitazone and 56 patients to metformin and sitagliptin. One patient in the rosiglitazone group withdrew for hypoglycemia, but it is not clearly reported how many in each group experienced hypoglycemia.[186] One study compared mild hypoglycemia in a metformin plus pioglitazone arm with a metformin plus sitagliptin arm at 26 weeks.[188] There was one patient with an event in the metformin plus pioglitazone arm and five patients with events in the metformin plus sitagliptin arm. This study also evaluated severe hypoglycemia, finding no events in either arm. A prospective cohort study also assessed severe hypoglycemia; no patients with these events were recorded.[262] (SOE: Low; Neither favored for mild, moderate, or total hypoglycemia) (SOE: Moderate; Neither favored for severe hypoglycemia)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Two short RCTs compared metformin plus a thiazolidinedione with metformin plus a GLP-1 receptor agonist, showing few differences between-group in hypoglycemia risk. The first 20-week study randomized 45 patients to metformin and rosiglitazone and 45 patients to metformin and exenatide, at comparable doses.[189] No patients receiving metformin plus rosiglitazone reported hypoglycemia, and two patients receiving metformin plus exenatide reported hypoglycemia, although this difference was not statistically significant.[189] There were no severe hypoglycemic events in this study. The second 26-week study randomized 325 patients to either metformin and pioglitazone or metformin and exenatide, at comparable doses.[188] The study reported one patient with mild hypoglycemia in the metformin plus pioglitazone arm and two patients with mild hypoglycemia in the metformin plus exenatide arm. The study also reported that no patients had severe hypoglycemia in either arm. (SOE: Low; Neither favored for mild, moderate, total, or severe hypoglycemia)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

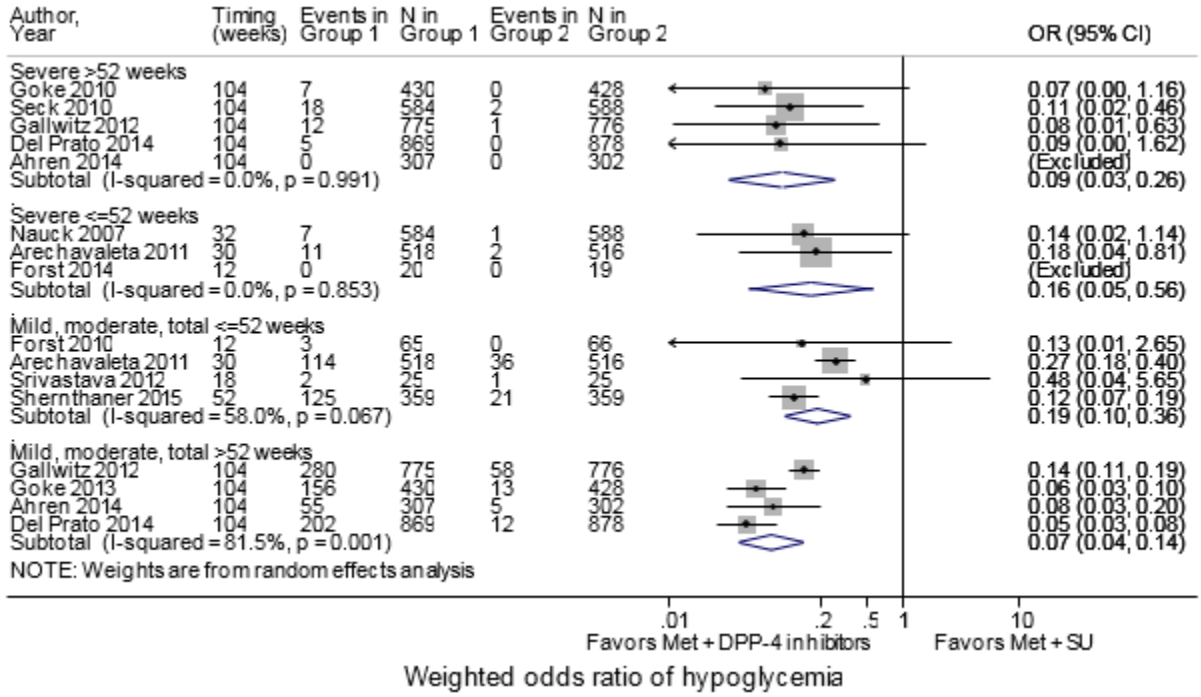
Eleven studies of the comparison of a combination of metformin plus a sulfonylurea versus a combination of metformin plus a DPP-4 inhibitor found more patients with severe and non-severe hypoglycemia in the metformin plus sulfonylurea arms compared with the metformin plus DPP-4 inhibitor arms (Figure 65).[139, 141, 190-197, 263]

Five studies, each lasting 2 years, reported on the outcome of severe hypoglycemia, favoring metformin plus a DPP-4 inhibitor over metformin plus a sulfonylurea (pooled OR, 0.09; 95% CI, 0.03 to 0.26).[141, 194-197] Similarly, three studies, each lasting less than 1 year, reported on the outcome of severe hypoglycemia, favoring metformin plus a DPP-4 inhibitor over metformin plus a sulfonylurea (pooled OR, 0.16; 95% CI, 0.05 to 0.56).[190-192] The range in RD for severe hypoglycemia in the shorter and longer studies was 0% to 3%.

Four additional studies were pooled for a meta-analysis of hypoglycemia (defined as mild, moderate, or total) with followup of 12 to 52 weeks. The pooled odds ratio was 0.19 (95% CI, 0.10 to 0.36), favoring metformin plus a DPP-4 inhibitor.[139, 190, 193, 263] Four longer studies, each with followup of 2 years, reported on mild, moderate, or total hypoglycemia, with all four studies

reporting significantly less hypoglycemia in the metformin plus DPP-4 inhibitor arms compared with the metformin plus sulfonylurea arms (pooled OR, 0.07; 95% CI, 0.04 to 0.14).[141, 194, 195, 197] For all meta-analyses, no single study markedly influenced the results. Only one meta-analysis had substantial heterogeneity, yet the point estimates were fairly similar among these studies. (SOE: High; Combination of metformin plus a DPP-4 inhibitor favored for mild, moderate, total, or severe hypoglycemia in shorter studies (<1 year) and longer studies (lasting 2 years)

Figure 65. Pooled odds ratio of hypoglycemia comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor, stratified by study duration and severity of hypoglycemia



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; Met = metformin; OR = odds ratio; SU - sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.
* The profile likelihood estimate provided a similar result.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

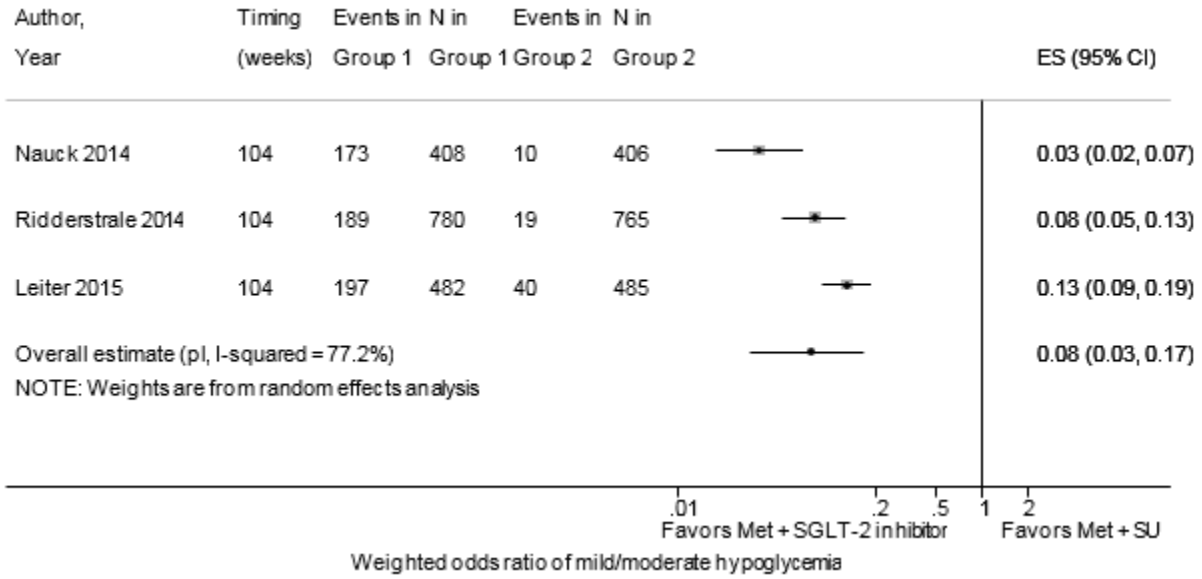
For the combined outcome of mild or total hypoglycemia, and for severe hypoglycemia, the comparison of a combination of metformin plus a sulfonylurea versus a combination of metformin plus a SGLT-2 inhibitor favored the metformin plus SGLT-2 inhibitor combinations over the combination of metformin plus a sulfonylurea.

Three 2-year studies were pooled, assessing mild or total hypoglycemia for this comparison.[199-201] The weighted odds ratio was 0.08 (95% CI, 0.03 to 0.17), favoring metformin plus SGLT-2 inhibitor combinations. There was substantial heterogeneity for this meta-analysis (I-squared, 83%); however, point estimates were fairly similar among the trials (Figure 66). Two

of the three studies used equipotent drug dosing between the treatment arms.[199, 201] One study mildly underdosed the metformin plus sulfonylurea arm (mean glimepiride dose of 2.7 mg) in comparison with the SGLT-2 inhibitor arm.[200] No single study strongly influenced the meta-analysis results. Two of these studies reported hypoglycemia in shorter (52-week) and longer (208-week) studies with similar findings favoring the metformin plus SGLT-2 inhibitor comparison.[54, 198]

Two of these trials also assessed severe hypoglycemia for this comparison (range in RD 1% to 3%).[198, 199] As above, the combination of metformin plus a SGLT-2 inhibitor was favored in both studies. The first RCT assessed severe hypoglycemia at 52 weeks in 965 randomized patients.[198] There were 15 patients with a severe hypoglycemic event in the metformin plus sulfonylurea arm and two patients in the metformin plus SGLT-2 inhibitor arm. The second RCT assessed severe hypoglycemia at 104 weeks in 814 randomized patients.[199] Severe hypoglycemic events were reported in 7 percent of patients in the metformin plus sulfonylurea arm and 1.7 percent of patients in the metformin plus SGLT-2 inhibitor arm. In two extension studies, lasting 2 and 4 years, the findings were similar, favoring the combination of metformin plus a SGLT-2 inhibitor.[54, 201] (SOE: High; Combination of metformin plus a SGLT-2 inhibitor favored for mild, moderate, or total hypoglycemia) (SOE: Moderate; Combination of metformin plus a SGLT-2 inhibitor favored for severe hypoglycemia)

Figure 66. Pooled odds ratio of mild or moderate hypoglycemia comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor*



CI = confidence interval; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; Met = metformin; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea

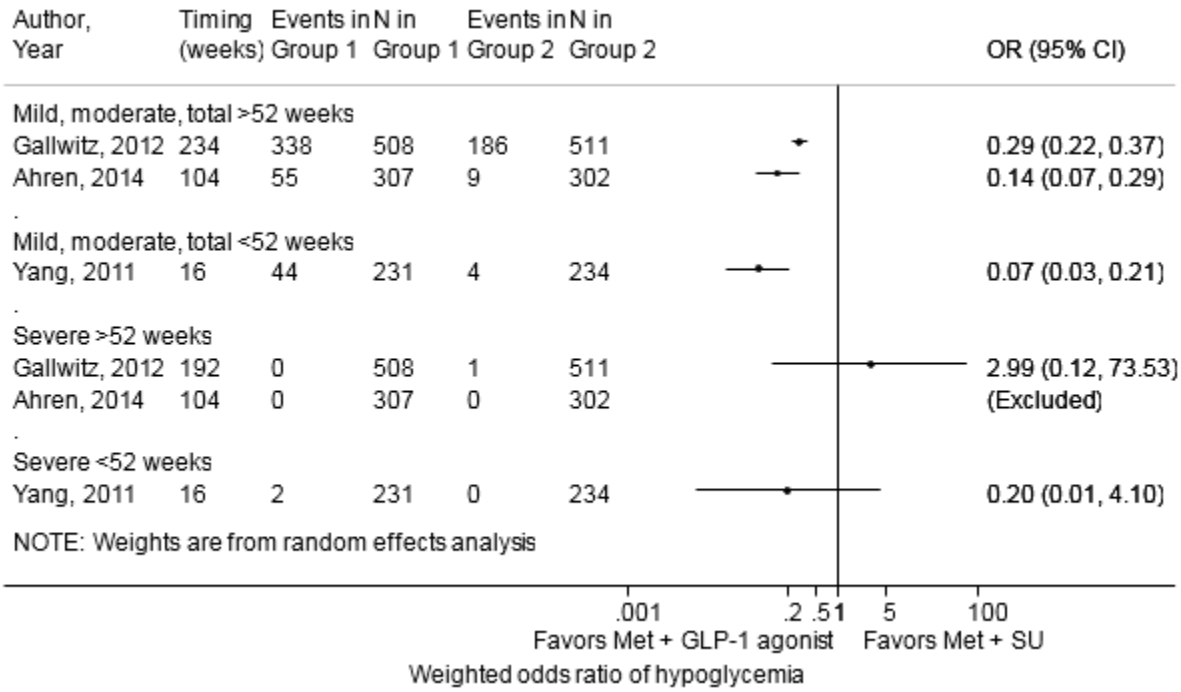
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

* The profile likelihood estimate provided a similar result.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Three RCTs compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a GLP-1 receptor agonist, showing a lower risk of total/mild/moderate hypoglycemia with the combination of metformin plus a GLP-1 receptor agonist (range in RD -15% to -30%) and no clear between-group differences in severe hypoglycemia risk (Figure 67).[53, 141, 204] No meta-analysis could be conducted for this comparison because of differences in study duration and hypoglycemia definitions. In all studies, glimepiride was the sulfonylurea given in combination with metformin. (SOE: Moderate; Combination of metformin plus a GLP-1 receptor agonist favored for mild, moderate, or total hypoglycemia) (SOE: Low, Neither favored for severe hypoglycemia)

Figure 67. Odds ratio of hypoglycemia comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a GLP-1 receptor agonist, stratified by study duration and severity of hypoglycemia



CI = confidence interval; GLP-1 = glucagon-like peptide-1; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a glucagon-like peptide-1 agonist; Met = metformin; OR = odds ratio; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a Basal Insulin

One study addressed the comparison of a combination of metformin plus a sulfonylurea versus a combination of metformin plus a basal insulin, favoring metformin and insulin glargine. This 48-week RCT compared metformin and glimepiride with metformin and insulin glargine.[206] While patients continued on the same pre-study dose of metformin of around 1500 mg, both the sulfonylurea and the insulin glargine were titrated to reach blood sugar targets. Nineteen patients

of 30 (63%) in the metformin plus glimepiride arm had mild hypoglycemia compared with 10 of 34 (29%) in the metformin plus insulin glargine arm. No severe hypoglycemia events occurred in either treatment arm. (SOE: Low; Combination of metformin plus basal insulin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither arm favored for severe hypoglycemia)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a Premixed Insulin

Two RCTs compared metformin plus sulfonylurea with metformin plus a premixed insulin, showing no clear between-group differences in hypoglycemia risk (Table 66).[207, 208] (SOE: Low; Neither favored for mild, moderate, or total hypoglycemia) (SOE: Insufficient for severe hypoglycemia)

Table 66. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a premixed insulin on hypoglycemia

Author, Year	Followup	Comparison	Outcome	Results
Malone, 2003[207]	16 weeks	Metformin + glargine versus metformin + lispro 75/25	Nocturnal	(N = 597 in trial) Greater number of participants with nocturnal hypoglycemia (p < 0.01) with metformin plus sulfonylurea than metformin plus insulin
			Severe	Comparable number with severe hypoglycemia (p=0.10)
Kvapil, 2006[208]	16 weeks	Metformin + glibenclamide versus metformin + aspart 70/30	Mild or moderate	9/114 versus 13/108; RR = 1.5 (95% CI, 0.7 to 3.4)

CI = confidence interval; RR = relative risk

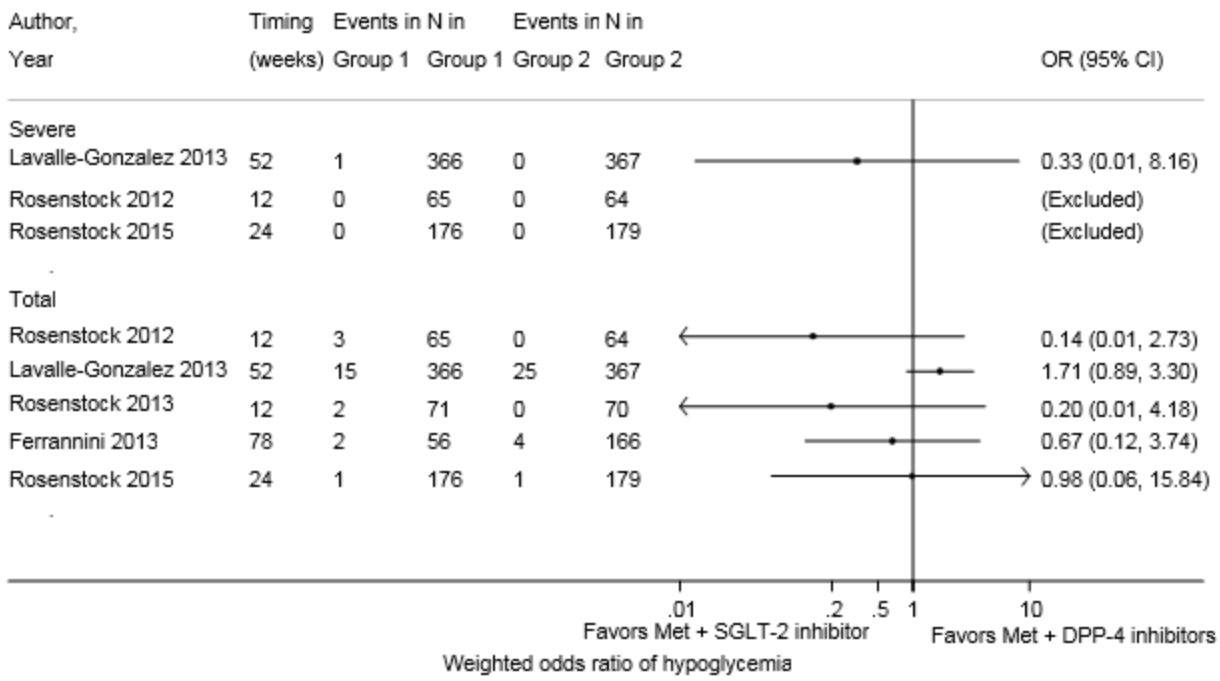
Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Five studies considered hypoglycemia for the comparison of a combination of metformin plus a DPP-4 inhibitor versus a combination of metformin plus a SGLT-2 inhibitor, showing no clear between-group differences in hypoglycemia risk (Figure 68). Four RCTs, with equipotent doses in each arm, showed no significant between-group differences in severe hypoglycemia risk.[156, 158, 209]

One 52-week RCT[158] randomized 714 patients to metformin plus sitagliptin or metformin plus canagliflozin, finding 4.1 percent of patients in the metformin plus sitagliptin arm with any hypoglycemic event compared with 6.8 percent of patients in the metformin plus canagliflozin arm. A 78-week, lower-quality RCT[90] found 3.6 percent of patients with any hypoglycemic event in the metformin plus sitagliptin arm, 1.8 percent of patients with such events in the low-dose metformin plus empagliflozin arm, and 2.4 percent of patients in the high-dose metformin plus empagliflozin arm.

Two shorter RCTs assessed total hypoglycemia with followup at 12 weeks, showing a non-significant greater risk of total hypoglycemia in the metformin plus DPP-4 inhibitor arms.[153, 156] (SOE: Low; Neither arm favored for mild, moderate, total, and severe hypoglycemia)

Figure 68. Odds ratio of hypoglycemia comparing a combination of metformin plus an SGLT-2 inhibitor with a combination of metformin plus a DPP-4 inhibitor, stratified by severity of hypoglycemia



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; Met = metformin; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Three studies reported on hypoglycemia for this comparison, showing no clear between-group differences in hypoglycemia risk (Table 67).[141, 159, 188] All three studies compared metformin plus sitagliptin, but each of the studies used a different GLP-1 receptor agonist in the metformin plus GLP-1 receptor agonist comparator arm (albiglutide, exenatide, and dulaglutide). None of the three studies had any severe hypoglycemia in either arm. For mild to moderate hypoglycemia, there were conflicting results with two of the three studies favoring the metformin plus DPP-4 inhibitor arms. This may be due to different types of GLP-1 receptor agonists, although there may be unidentified sources of heterogeneity, too. (SOE: Low; Neither arm favored for mild, moderate, total, and severe hypoglycemia)

Table 67. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 receptor agonist on hypoglycemia

Author, Year	Followup (Weeks)	Metformin + DPP-4 Inhibitor (Dose*)	Metformin + GLP-1 Receptor Agonist (Dose*)	Definition of Hypoglycemia	Results† (Metformin + DPP-4 Inhibitor Vs Metformin + GLP-1 Receptor Agonist)
Ahren, 2014[141]	104	Metformin (fixed at ≥ 1500 mg) + sitagliptin (fixed at 100 mg)	Metformin (fixed at ≥ 1500 mg) + albiglutide (max 50 mg weekly)	Mild-moderate (asymptomatic, but BG ≤ 3.9 mmol/L) Mild-moderate (symptomatic and BG ≤ 3.9 mmol/L) Severe (required third party assistance)	4/302 (1.3%) vs 4/302 (1.3%) 5/302 (1.7%) vs 9/302 (3%) 0/302 (0%) vs 0/302 (0%)
Bergenstal, 2010[188]	26	Metformin (fixed, mean 1583 mg) + sitagliptin (fixed at 100 mg)	Metformin (fixed, mean 1504 mg) + exenatide (fixed at 2 mg weekly)	Mild-moderate (symptomatic and BG < 3 mmol/L) Severe‡	5/166 (3%) vs 2/160 (1.3%) 0/166 (0%) vs 0/160 (0%)
Nauck, 2014[159]	52	Metformin (fixed at ≥ 1500 mg) + sitagliptin (fixed at 100 mg)	Metformin (fixed at ≥ 1500 mg) + dulaglutide (fixed 0.75 mg weekly)	Mild-moderate (signs, symptoms and/or BG ≤ 70 mg/dL) Severe (required third party assistance)	15/315 (4.8%) vs 16/302 (5.3%) 0/315 (0%) vs 0/302 (0%)
		Metformin (fixed at ≥ 1500 mg) + sitagliptin (fixed at 100 mg)	Metformin (fixed at ≥ 1500 mg) + dulaglutide (fixed 1.5 mg weekly)	Mild-moderate (signs, symptoms and/or BG ≤ 70 mg/dL) Severe (required third party assistance)	15/315 (4.8%) vs 31/304 (10.2%) 0/315 (0%) vs 0/304 (0%)

BG = blood glucose; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; max = maximum; mg = milligrams; mg/dL = milligrams per deciliter; mmol/L = millimole per liter

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

‡ Severe hypoglycemia was defined as a loss of consciousness, seizure, or coma that resolved after treatment with glucagon or glucose, or severe impairment that required third-party assistance to resolve the episode and a blood glucose concentration of lower than 3 mmol/L.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a Basal Insulin

One RCT assessed hypoglycemia for the comparison of a combination of metformin plus a DPP-4 inhibitor versus a combination of metformin plus a basal insulin, finding more hypoglycemic events in the metformin plus insulin arm (Table 68).[211] (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 68. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a basal insulin on hypoglycemia

Author, Year	Followup (Weeks)	Metformin + DPP-4 Inhibitor (Dose*)	Metformin + Basal Insulin (Dose*)	Definition of Hypoglycemia	Results† (Metformin + DPP-4 Inhibitor Vs Metformin + Basal Insulin)
Aschner, 2012[211]	24	Metformin (baseline dose 1835 mg) + sitagliptin (fixed at 100 mg)	Metformin (baseline dose 1852 mg) + insulin glargine (max 0.5 U/kg)	Severe (severe symptomatic) Total (symptomatic and BG ≤ 3.9 mmol/L)	1/264 (0.4%) vs 3/237 (1.3%) 28/264 (10.6%) vs 86/237 (36.3%)

BG = blood glucose; DPP-4 = dipeptidyl peptidase-4; max = maximum; mg = milligrams; mmol/L = millimole per liter; U/kg = units per kilogram

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

Combination of Metformin Plus a GLP-1 Receptor Agonist Versus a Combination of Metformin Plus a Basal Insulin

Two RCTs compared metformin plus basal insulin with the combination of metformin plus exenatide, with lower risk of mild or moderate hypoglycemia in the metformin plus exenatide arms in both studies (range in RD of -3% to -25%) (Table 69).[212, 264] Both RCTs reported no between-group differences in severe hypoglycemia.[212, 264] (SOE: Low; Combination of metformin plus a GLP-1 receptor agonist favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Table 69. Randomized controlled trials comparing a combination of metformin plus a GLP-1 receptor agonist with a combination of metformin plus a basal insulin on hypoglycemia

Author, Year	Followup (Weeks)	Metformin + GLP-1 (Dose*)	Metformin + Basal Insulin (Dose*)	Definition of Hypoglycemia	Results† (Metformin + GLP-1 Vs Metformin + Basal Insulin)
Davies, 2013[264]	26	Metformin (fixed at ≥ 1000 mg) + exenatide (fixed at 2 mg weekly)	Metformin (fixed at ≥ 1000 mg) + insulin detemir (mean initial dose 0.21 IU/kg; mean end dose 20.8 IU, end dose 0.51 IU/kg)	Mild-moderate (symptoms that were self-treated or resolved on their own, with documented BG < 3.0 mmol/L) Severe hypoglycemia‡	0/33 (0%) vs 1/29 (3.4%) 0/33 (0%) vs 0/29 (0%)
Diamant, 2010[212]	84	Metformin (continued stable dose) + exenatide (fixed at 2 mg weekly)	Metformin (continued stable dose) + insulin glargine (started at 10 IU then titrate to glycemic goal of 4-5.5 mmol/L)	Mild-moderate (symptoms and BG < 3.0 mmol/L and was either self-treated or resolved independently) Severe hypoglycemia‡	13/164 (7.9%) vs 51/157 (32.5%) 1/164 (0.6%) vs 1/157 (0.6%)

BG = blood glucose; GLP-1 = glucagon-like peptide-1 receptor agonist; IU = international units; IU/kg = international units per kilogram; mg = milligrams; mmol/L = millimole per liter;

* All doses were titrated, unless otherwise stated.

† Results are presented as n/N (%) unless otherwise stated.

‡ Any hypoglycemic episode with symptoms consistent with hypoglycemia that led to loss of consciousness or seizure, with prompt recovery in response to glucagon or glucose administration, or documented hypoglycemia [blood glucose <3.0mmol] necessitating assistance of another person

Combination of Metformin Plus a GLP-1 Receptor Agonist Versus a Combination of Metformin Plus a Premixed Insulin

One study assessed the comparison of a combination of metformin plus a GLP-1 receptor agonist versus a combination of metformin plus a premixed insulin, showing less hypoglycemia in the metformin plus GLP-1 receptor agonist arm compared with the metformin plus premixed insulin arm. This 26-week RCT found an incidence of first hypoglycemic episodes of 8.0 percent in the metformin plus exenatide group versus 20.5 percent in the metformin plus insulin aspart 70/30 group (RD, -12.5%).[213] No severe hypoglycemia was reported. (SOE: Low; Combination of metformin plus a GLP-1 receptor agonist favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither favored for severe hypoglycemia)

Combination of Metformin Plus a Basal Insulin Versus a Combination of Metformin Plus a Premixed Insulin

Five trials examined the comparison of metformin plus basal insulin to metformin plus a mix of long- and short-acting insulin, consistently favoring the former (range in RD, -5% to -28%) (Table 70).[214-216, 223, 224] Due to the heterogeneity of these trials (I-squared, 78.8%), they were not pooled in a meta-analysis. The heterogeneity may be owing to the difference in followup times, insulin preparations, and insulin dosing. (SOE: Moderate; Combination of metformin plus a basal insulin favored for mild, moderate, or total hypoglycemia) (SOE: Low; Neither arm favored for severe hypoglycemia)

Table 70. Randomized controlled trials comparing a combination of metformin plus a basal insulin with a combination of metformin plus a premixed insulin on hypoglycemia

Author, Year	Comparison	Outcome	Results	RR and Comments (Combination Metformin and Another Insulin as Reference Group)
Malone, 2004[223]	Metformin + glargine versus metformin + lispro 75/25	Mild or moderate at 32 weeks	40/101 versus 57/100 (87 versus 181 events)	RR = 0.69 (95% CI 0.5 to 0.9), both arms of cross-over pooled
		Severe at 32 weeks	None	NA
Malone, 2005[224]	Metformin + glargine versus metformin + lispro 75/25	Mild or moderate at 32 weeks	0.44 versus 0.61 events/patient/30 days	P = 0.47; more daytime hypoglycemia with lispro 75/25 but less nocturnal hypoglycemia
		Severe at 32 weeks	None	NA
Raskin, 2007[215]	Metformin + glargine versus metformin + aspart 70/30	Mild or moderate at 28 weeks	11/78 versus 33/79 (23 versus 121 events)	RR = 0.34 (95% CI 0.2 to 0.6)
Robbins, 2007[214]	Metformin + glargine versus metformin + lispro 50/50	Mild or moderate at 24 weeks	75/158 versus 79/157	RR = 0.94 (95% CI 0.8 to 1)
		Severe at 24 weeks	2/158 versus 3/157	RR = 0.66 (95% CI 0.1 to 4)
Davies, 2007[216]	Metformin + NPH versus metformin + NPH/regular 70/30	Mild or moderate	7/29 versus 8/27	RR = 0.81 (95% CI 0.34 to 1.9); a poorly conducted trial

CI = confidence interval; NA = not available; NPH = neutral protamine Hagedorn; RR = relative risk

Strength of Evidence for Hypoglycemia

As noted in the Key Points, Table 71, Table 72, and Table 73, we found moderate or high strength of evidence for many of the monotherapy comparisons evaluating hypoglycemia and also found a number of combination comparisons with high or moderate strength of evidence. We found several comparisons of interest for which there was no or minimal evidence, especially among the combination comparisons. Study limitations for most comparisons were low or medium, with only two comparisons having high study limitations owing to lack of blinding, lack of description of withdrawals and dropouts, or high losses to followup. In general, we did not find strong differences in outcomes in the lower- versus higher-quality studies. When we found low strength of evidence for hypoglycemia, this tended to occur in the setting of fair to poor study quality and inconsistency for monotherapy comparisons and was related to insufficient data in the combination comparisons. We generally found consistency among studies if there were more than three studies for a given comparison. Most evidence on hypoglycemia was precise for monotherapy comparisons; there was less precision when there were fewer studies, as in the combination comparisons. We did not find any evidence of publication bias using the Begg's and Egger's test for the comparisons with greater than ten studies. We identified unpublished studies that could have influenced our rating of the evidence. A single unpublished study found more hypoglycemia in a DPP-4 inhibitor arm than in the comparator metformin arm; this was consistent with our findings and could have strengthened the evidence. Also, we identified two additional studies of the comparison of sulfonylurea to DPP-4 inhibitor monotherapy which were consistent with the published studies; the addition of this evidence may have allowed us to rate the strength of evidence as high for this comparison.

Table 71. Strength of evidence domains for monotherapy comparisons in terms of hypoglycemia among adults with type 2 diabetes

Comparison*	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. TZD	Mild, moderate, total	5 (4,197)	Medium	Inconsistent	Direct	Precise	Undetected	Low	Metformin favored
	Severe	1 (409)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. SU	Mild, moderate, total	RCTs: 14 (7,332)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin favored; 4.0 (1.8 to 9.8)
		Observational: 1 (1789)	Medium	Unknown	Direct	Precise	n/a		
	Severe	2 (376)	Low	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin favored; range in OR, 0.49 to 0.71; range in RD, -1% to -23%
Metformin vs. DPP-4 inhibitors	Mild, moderate, total	6 (6,710)	High	Consistent for symptomatic hypoglycemia	Direct	Precise	Undetected	Low	DPP-4 inhibitor favored
	Severe	6 (6,710)	High	Inconsistent	Direct	Imprecise	Suspected	Low	Neither favored
Metformin vs. SGLT-2 inhibitors	Mild, moderate, total	5 (2,700)	Medium	Consistent	Direct	Precise	Undetected	Moderate	SGLT-2 inhibitors favored; 0.5 (0.2 to 1.3)
	Severe	2 (831)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. GLP-1 receptor agonists	Mild, moderate, total	3 (1360)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Metformin favored
	Severe	3 (1360)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored

Table 71. Strength of evidence domains for monotherapy comparisons in terms of hypoglycemia among adults with type 2 diabetes (continued)

Comparison*	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
TZD vs. SU	Mild, moderate, total	8 (6,212)	Low	Consistent	Direct	Precise	Undetected	High	TZD favored; 6.3 (4.1 to 9.8)
	Severe	2 (3,304)	Low	Consistent	Direct	Precise	Undetected	Moderate	TZD favored; OR, 8.1; RD, 0.4%
TZD vs. DPP-4 inhibitors	Mild, moderate, total	3 (1,686)	Low	Inconsistent	Direct	Precise	Undetected	Insufficient	Unable to determine
	Severe	2 (653)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
TZD vs. GLP-1 receptor agonists	Mild, moderate, total	2 (689)	Medium	Consistent	Direct	Imprecise	Undetected	Low	TZD favored
	Severe	1 (411)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
SU vs. DPP-4 inhibitors	Mild, moderate, total	4 (1,065)	Medium	Consistent	Direct	Precise	Undetected	Moderate	DPP-4 favored; range in OR, 3.8 to 12.4; range in RD, 6% to 15%
	Severe	2 (623)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	DPP-4 favored
SU vs. GLP-1 receptor agonists	Mild, moderate, total	5 (2,467)	Medium	Consistent	Direct	Precise	Undetected	Moderate	GLP-1 favored for mild-moderate hypoglycemia; range in OR, 3.1 to 5.3; range in RD, 12% to 21%
	Severe	3 (1546)	High	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
DPP-4 inhibitors vs. SGLT-2 inhibitors	Mild, moderate, total	1 (670)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
	Severe	1 (670)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored

Table 71. Strength of evidence domains for monotherapy comparisons in terms of hypoglycemia among adults with type 2 diabetes (continued)

Comparison*	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
DPP-4 inhibitors vs. GLP-1 receptor agonists	Mild, moderate, total	1 (411)	Low	Unknown	Direct	Imprecise	Undetected	Low	DPP-4 favored
	Severe	1 (411)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored

CI = confidence interval; DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; OR = odds ratio; RD = risk difference; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) due to the few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Table 72. Strength of evidence domains for metformin versus metformin-based combination comparisons in terms of hypoglycemia among adults with type 2 diabetes

Comparison*	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + TZD	Mild, moderate, total	10 (3,906)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin favored; 1.6 (0.99 to 2.4)
Metformin vs. metformin + SU	Mild, moderate, total	12 (3,732)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin favored, range in OR, 0.99 to 28.55; range in RD, 0% to 35%
	Severe	2 (544)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + DPP-4 inhibitors	Mild, moderate, total	27 (17,946)	Low	Consistent	Direct	Precise	Undetected	High	Neither favored; pooled OR for mild-moderate, 0.97 (0.6 to 1.5) Pooled OR for total, 1.0 (0.6 to 1.7
	Severe	12 (5,674)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + SGLT-2 inhibitors (<2 years)	Mild, moderate, total	10 (6,178)	Low	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin favored; 1.7; 95% CI, 0.8 to 3.7
	Severe	7 (2,934)	Low	Consistent	Direct	Imprecise	Undetected	Moderate	Neither favored; no events
Metformin vs. metformin + GLP-1 receptor agonists	Mild, moderate, total	4 (2,654)	High	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
	Severe	2 (1,186)	High	Consistent	Direct	Imprecise	Undetected	Low	Neither favored

CI = confidence interval; DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; OR = odds ratio; RD = risk difference; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Table 73. Strength of evidence domains for metformin-based combination comparisons in terms of hypoglycemia among adults with type 2 diabetes

Comparison*	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + TZD vs. metformin + SU	Mild, moderate, total	7 (975)	Medium	Consistent	Direct	Imprecise	Undetected	High	Metformin + TZD favored; 7.5 (4.0 to 13.8)
	Severe	1 (314)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin + TZD favored
Metformin + TZD vs. metformin + DPP-4 inhibitors	Mild, moderate, total	2 (603)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither drug combination favored
	Severe	RCT 1 (491) Obs 1 (83)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + TZD vs. metformin + GLP-1 receptor agonists	Mild, moderate, total	2 (415)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither drug combination favored
	Severe	2 (415)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither drug combination favored
Metformin + SU vs. metformin + DPP-4 inhibitors	Mild, moderate, total	10 (6,757)	Medium	Consistent	Direct	Imprecise	Undetected	High	Metformin + DPP4-inhibitors favored Pooled OR for studies ≤52 weeks: 0.2 (0.1 to 0.4) Pooled OR for studies >52 weeks: 0.1 (0.04 to 0.14)
	Severe	6 (4,717)	Medium	Consistent	Direct	Imprecise	Undetected	High	Metformin + DPP-4 inhibitors favored Pooled OR for studies <52 weeks: 0.2 (0.1 to 0.6) Pooled OR for studies ≥52 weeks: 0.1 (0.03 to 0.3)

Table 73. Strength of evidence domains for metformin-based combination comparisons in terms of hypoglycemia among adults with type 2 diabetes (continued)

Comparison*	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + SU vs. metformin + SGLT-2 inhibitors (< 2 years)	Mild, moderate, total	3 (3,815)	Low	Consistent	Direct	Precise	Undetected	High	Metformin + SGLT-2 inhibitors favored; 0.1 (0.03 to 0.2)
	Severe	2 (1,779)	Low	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin + SGLT-2 inhibitors favored in studies lasting 1-2 years; range in OR, 0.13 to 0.23; range in RD, -3% to -1%
Metformin + SU vs. metformin + GLP-1 receptor agonists	Mild, moderate, total	3 (2,557)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + GLP-1 inhibitor favored in studies lasting 16 to 238 weeks; range in OR, 0.07 to 0.29; range in RD, -30% to -15%
	Severe	3 (2,557)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + SU vs. metformin + basal insulin	Mild, moderate, total	1 (75)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin + insulin favored
	Severe	1 (75)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither arm favored
Metformin + SU vs. metformin + premixed insulin	Mild, moderate, total	2 (827)	Medium	Consistent	Direct	Imprecise	Suspected	Low	Neither arm favored
	Severe	1 (597)	High	Unknown	Direct	Imprecise	Suspected	Insufficient	Unable to draw a conclusion
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Mild, moderate, total	4 (2,889)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither arm favored in studies lasting 12 to 78 weeks
	Severe	2 (1,359)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither arm favored

Table 73. Strength of evidence domains for metformin-based combination comparisons in terms of hypoglycemia among adults with type 2 diabetes (continued)

Comparison*	Outcome	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 receptor agonists	Mild, moderate, total	3 (1,851)	Medium	Inconsistent	Direct	Precise	Undetected	Low	Neither arm favored in studies lasting 26 to 104 weeks
	Severe	3 (1,851)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither arm favored in studies lasting 26 to 104 weeks
Metformin + DPP-4 inhibitors vs. metformin + basal insulin	Mild, moderate, total	1 (515)	Medium	Unknown	Direct	Precise	Undetected	Low	Metformin + DPP-4 inhibitor favored
	Severe	1 (515)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither arm favored
Metformin + GLP-1 receptor agonists vs. metformin + basal insulin	Mild, moderate, total	2 (397)	Medium	Consistent	Direct	Imprecise	Undetected	Low‡	Metformin + GLP-1 receptor agonist favored in studies lasting 26 to 84 weeks
	Severe	2 (383)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither arm favored
Metformin + GLP-1 receptor agonists vs. metformin + premixed insulin	Mild, moderate, total	1 (363)	High	N/A	Direct	Imprecise	Undetected	Low‡	Metformin + GLP-1 receptor agonist favored
	Severe	1 (363)	High	Unknown	Direct	Imprecise	Undetected	Low	Neither arm favored
Metformin + basal insulin vs. metformin + premixed insulin	Mild, moderate, total	5 (530)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin + basal insulin favored; range in OR, 0.3 to 0.9; range in RD, -28% to -5%
	Severe	3 (613)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither arm favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; OR = odds ratio; RD = risk difference; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack

of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.
† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.
‡ If we compare the metformin plus GLP-1 receptor agonists versus metformin plus premixed or basal insulin, then metformin plus GLP-1 receptor agonists have less hypoglycemia over metformin plus either premixed or basal insulin with moderate strength of evidence

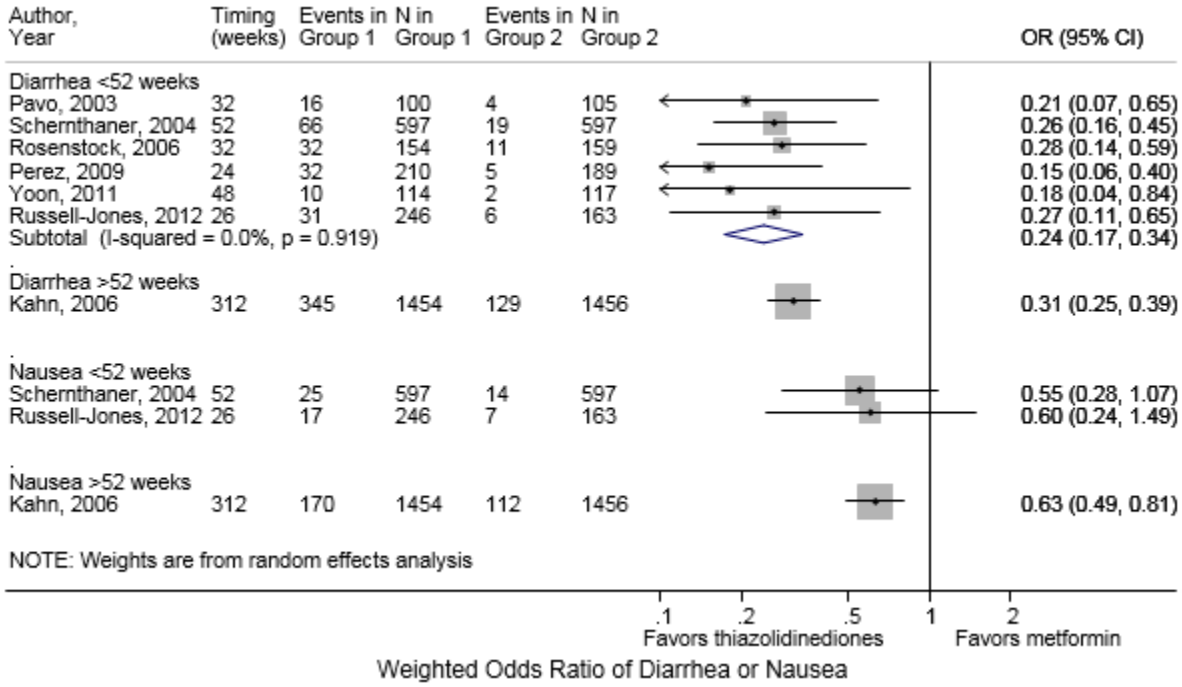
Evidence for Gastrointestinal Side Effects

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Eight RCTs compared GI adverse events between metformin and either pioglitazone or rosiglitazone.[50, 59, 62, 64, 67, 70, 73, 74] GI adverse events were more common with metformin compared with thiazolidinediones in the majority of RCTs, except for dyspepsia, where the number of events were comparable for both treatments. More people had diarrhea and nausea with metformin than thiazolidinediones (Figure 69). There were no overly influential studies in the meta-analysis for diarrhea, and there was little heterogeneity between these studies. (SOE: Moderate; Thiazolidinediones favored for diarrhea and nausea)

Figure 69. Pooled odds ratio of gastrointestinal adverse events comparing metformin with thiazolidinediones



CI = confidence interval; Group 1 = metformin; Group 2 = thiazolidinediones; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus Sulfonylureas

Twelve RCTs compared GI adverse events between metformin and a sulfonylurea.[50, 74, 129-131, 133, 134, 136-138, 251, 257] GI adverse events tended to be more common with metformin than with sulfonylurea (Table 74). Based on meta-analyses, there were fewer GI adverse events with sulfonylureas than with metformin for the outcomes of diarrhea (OR, 0.42; 95% CI, 0.24 to 0.72; I-squared, 48.4%; six studies), abdominal pain (OR, 0.44; 95% CI, 0.29 to 0.67; I-squared, 0%; three studies), nausea and vomiting (OR, 0.45; 95% CI, 0.31 to 0.65; I-squared, 0%; three

studies) and any GI adverse event (OR, 0.45; 95% CI, 0.28 to 0.72; I-squared, 22.2%; four studies). (SOE: Moderate; Sulfonylureas favored)

Table 74. Studies comparing metformin with sulfonylureas on gastrointestinal adverse events

Author, Year	Outcome	Event Rates (Metformin Versus Sulfonylureas)
Hermann, 1994[134]	Any GI outcome Abdominal pain Diarrhea Nausea Withdrawal for GI symptoms	63% (24/38) versus 32% (11/34) 18% (7/38) versus 6% (2/34) 50% (19/38) versus 0 (0/34) 24% (9/38) versus 9% (3/34) 14% versus 0%
DeFronzo, 1995[137]	Nausea and diarrhea	1.4% (3/210) versus 1.0% (2/209)
Amador-Licona, 2000[251]	Diarrhea and abdominal pain	14.3% (4/28) for metformin; event rates are not reported for sulfonylurea
Charpentier, 2001[136]	Diarrhea	7% (5/75) versus 1% (1/150)
Blonde, 2002[131]	Nausea and vomiting Dyspepsia/heartburn Flatulence	12.4% (19/153) versus 5.5% (9/164) 4.6% (7/153) versus 3% (5/164) 2% (3/153) versus 0% (0/164)
Garber, 2002[133]	 Any GI outcome Diarrhea Nausea/vomiting Abdominal pain Dyspepsia	Metformin (n = 159); glyburide (n = 160) 43% versus 24% 15.1% versus 4.4% 6.3% versus 0.6% 5% versus 3.1% 5% versus 2.5%
Garber, 2003[129]	Nausea/vomiting Abdominal pain Diarrhea	10.4% (17/164) versus 6.6% (10/151) 6.1% (10/164) versus 4% (6/151) 18% (30/164) versus 5.3% (18/151)
Goldstein, 2003[130]	Diarrhea	17.3% (13/75) versus 13.1% (11/84)
Derosa, 2004[257]	Nausea and diarrhea	2.4% (2/75) versus 0% (0/73)
Kahn, 2006[50]	Combined GI events Nausea Vomiting Diarrhea Abdominal discomfort	38% (557/1454) versus 22% (316/1441) 11.7% (170/1454) versus 6.9% (99/1441) 5.8% (84/1454) versus 3.1% (45/1441) 23.7% (345/1454) versus 9.9% (142/1441) 15.4% (224/1454) versus 11.3% (163/1441)
Chien, 2007[138]	Combined GI events	32% (8/25) versus 13% (3/23)
Yoon, 2011[74]	Diarrhea Discomfort, pain, nausea or vomiting	8.8% (10/114) versus 3.4% (4/118) 8.8% (10/114) versus 8.5% (10/118)

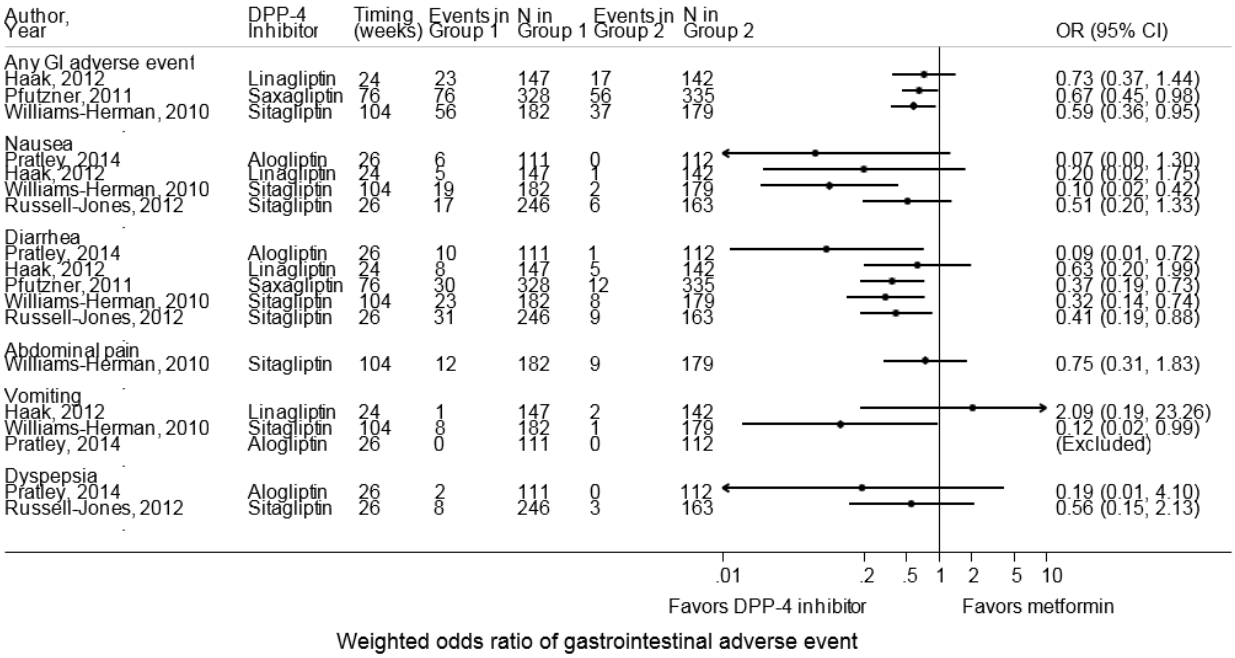
GI = gastrointestinal

Metformin Versus DPP-4 Inhibitors

Six RCTs compared metformin with a DPP-4 inhibitor and reported on GI adverse events.[73, 82, 84-87] Metformin had more GI adverse events compared with each of the DPP-4 inhibitors (Figure 70). One trial identified solely in ClinicalTrials.gov had results consistent with the published studies (NCT01076088). We combined the three studies with similar study durations and dosages for nausea and diarrhea. We did not combine "any" GI adverse event outcomes, because study durations were not sufficiently similar. Based on meta-analyses, there were fewer

nausea outcomes for DPP-4 inhibitors compared with metformin (pooled OR, 0.37; 95% CI, 0.15 to 0.91; I-squared, 4%; three studies) and fewer diarrhea outcomes for the same comparison (pooled OR, 0.38, 95% CI, 0.18 to 0.83; I-squared, 25%; three studies). The excluded longer studies were consistent with the findings, favoring DPP-4 inhibitors over metformin (Figure 70). (SOE: High; DPP-4 inhibitors favored)

Figure 70. Odds ratio of gastrointestinal adverse events comparing metformin with DPP-4 inhibitors



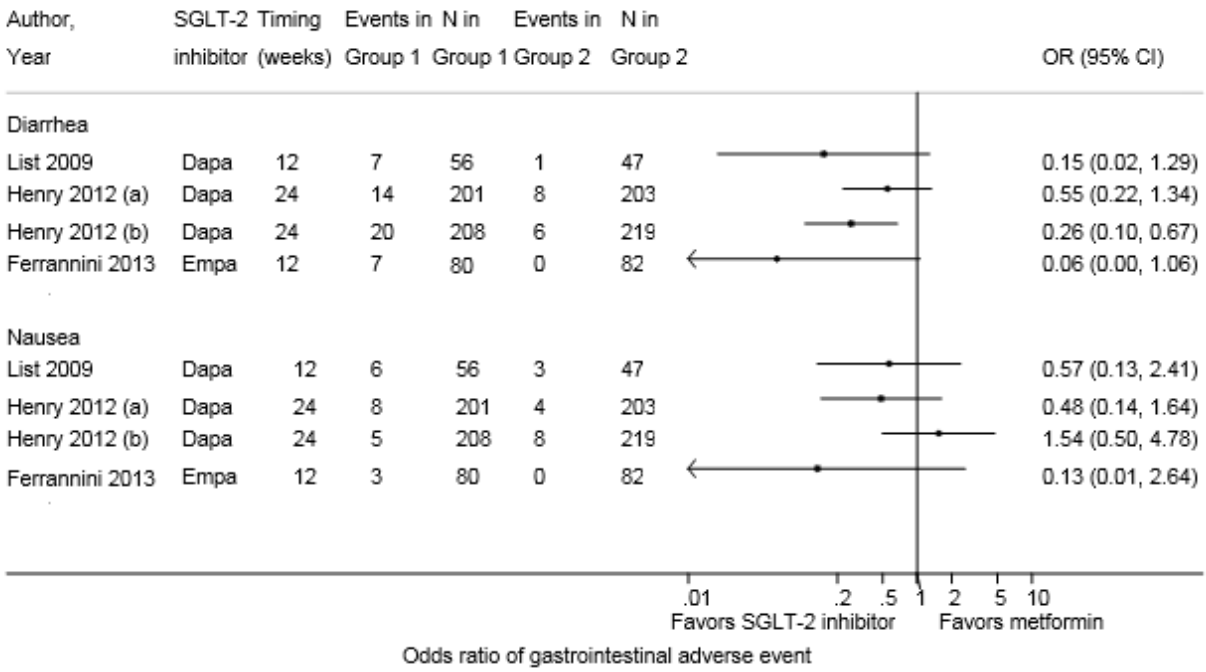
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = dipeptidyl peptidase-4 inhibitors; OR = odds ratio

Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Metformin Versus SGLT-2 Inhibitors

Three trials (published in two articles) compared metformin with dapagliflozin.[88, 89] One trial compared metformin with empagliflozin,[239] Diarrhea and nausea tended to be more common with metformin than with the SGLT-2 inhibitors (Figure 71). We did not pool the trials owing to dosage differences. (SOE: Low; SGLT-2 inhibitors favored for diarrhea and nausea)

Figure 71. Odds ratio of gastrointestinal adverse events comparing metformin with SGLT-2 inhibitors

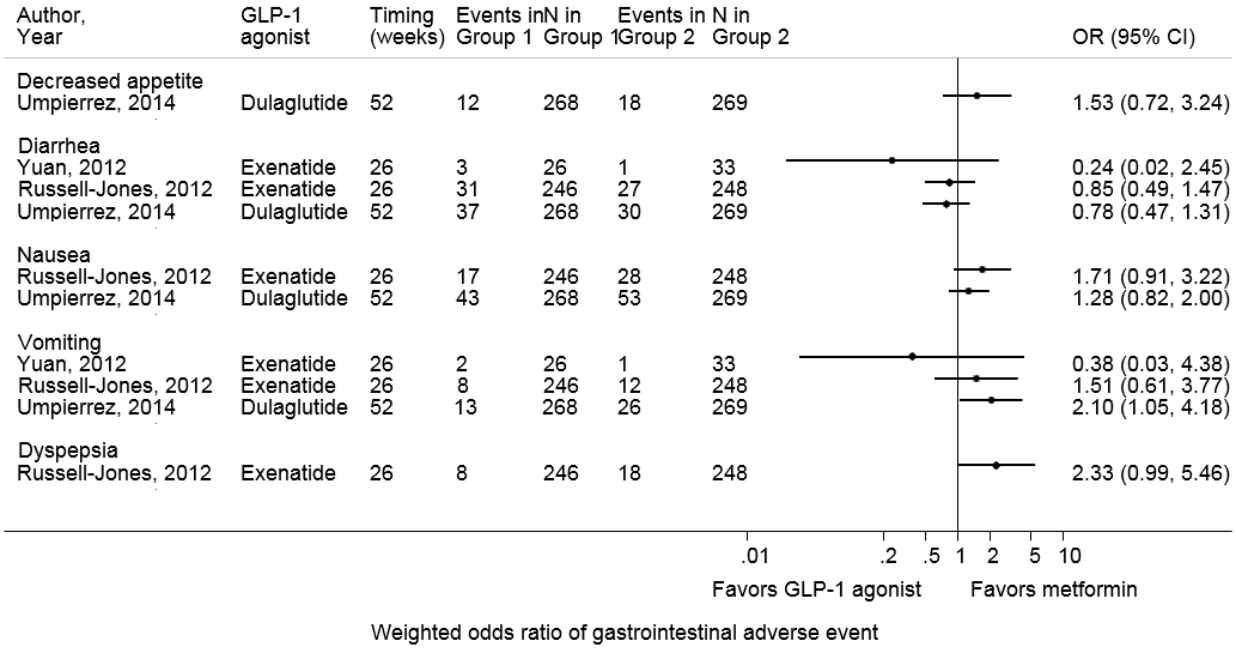


CI = confidence interval; Dapa = dapagliflozin; Empa = empagliflozin, Group 1 = metformin; Group 2 = sodium-glucose co-transporter-2 inhibitors; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Metformin Versus GLP-1 Receptor Agonists

Two trials compared metformin with exenatide.[73, 92] One trial compared metformin with once-weekly subcutaneously injected 0.75 mg or 1.5 mg of dulaglutide.[91] Diarrhea non-significantly differed between metformin and GLP-1 receptor agonists (OR, 0.78; 95% CI, 0.54 to 1.14; I-squared, 0%; three studies). However, nausea (OR, 1.28 and 1.71), vomiting (pooled OR, 1.73; 95% CI, 1.01 to 2.95; I-squared, 0%; three studies) and dyspepsia (OR, 2.33) were more common with the GLP-1 receptor agonists (Figure 72). (SOE: Low; GLP-1 receptor agonists favored for diarrhea; SOE: Moderate; Metformin favored for nausea/vomiting)

Figure 72. Odds ratio of gastrointestinal adverse events comparing metformin with GLP-1 receptor agonists



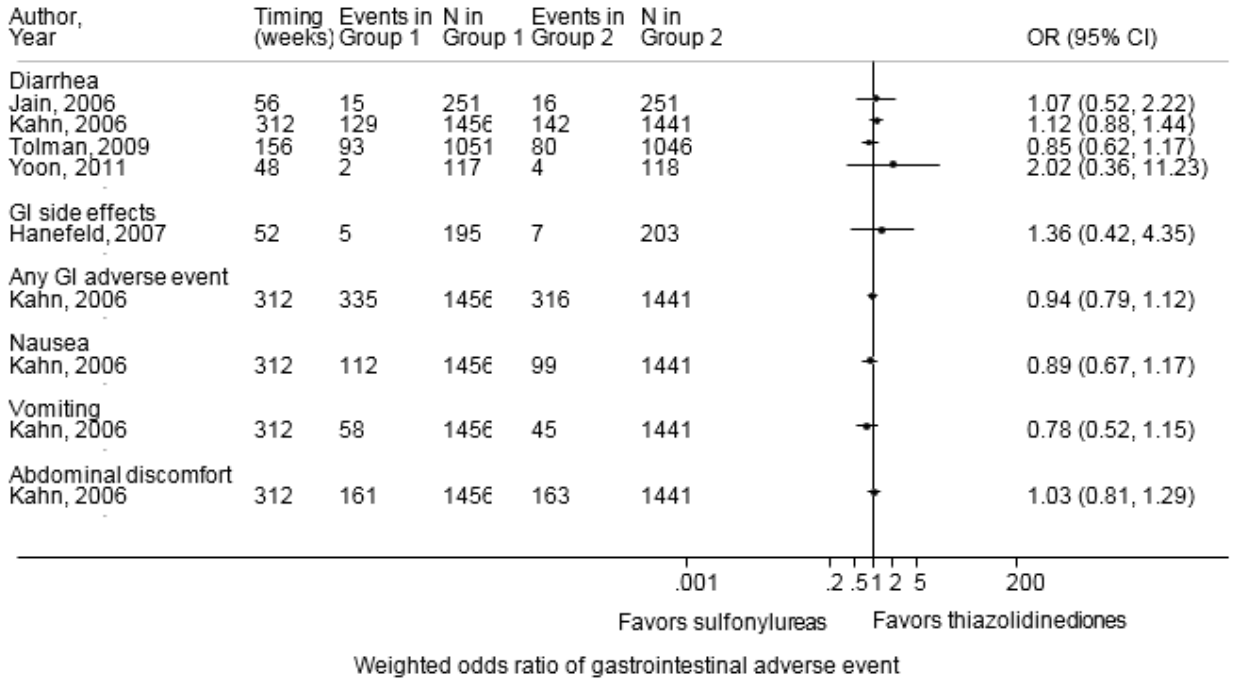
CI = confidence interval; GLP-1 = glucagon-like peptide-1; Group 1 = metformin; Group 2 = glucagon-like peptide-1 agonists; OR = odds ratio

Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Thiazolidinediones Versus Sulfonylureas

Five RCTs compared diarrhea occurrence with pioglitazone or rosiglitazone to either glyburide, glibenclamide or glimepiride and showed no differences between treatments (Figure 73).[50, 52, 74, 94, 95] The range in percentages of subjects with any type of GI adverse events in the thiazolidinediones (1% to 13%) was similar to the range with any type of GI adverse events in the sulfonylurea arms (1% to 18%), with a range in RD of -1.2% to 1.7%. Studies of diarrhea were not combined in a meta-analysis due to differences in study duration. (SOE: High; Neither favored)

Figure 73. Odds ratio of gastrointestinal adverse events comparing thiazolidinediones with sulfonylureas



CI = confidence interval; Group 1 = thiazolidinediones; Group 2 = sulfonylureas; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Thiazolidinediones Versus DPP-4 Inhibitors

Two trials compared pioglitazone with sitagliptin with no meaningful difference between treatments for GI adverse events.[48, 73]

One trial identified solely in ClinicalTrials.gov (NCT01183013) reported no cases of diarrhea or vomiting in any of the 134 participants receiving pioglitazone (45 mg daily) or the 130 participants receiving linagliptin (5 mg daily). (SOE: Low; Neither favored)

Thiazolidinediones Versus GLP-1 Receptor Agonists

Two trials compared pioglitazone with exenatide for outcomes of constipation, diarrhea, dyspepsia, nausea, and vomiting.[73, 105] Exenatide-treated participants tended to have more gastrointestinal side effects than those receiving pioglitazone, in both trials (range in RD 0.1% to 7% depending on the GI adverse event reported).

A trial identified in ClinicalTrials.gov (NCT01147627) reported significantly more GI adverse events with exenatide compared with pioglitazone (37/142 versus 1/136 for nausea; 15/142 versus 1/136 for vomiting; 6/142 versus 4/136 for diarrhea). (SOE: Low; Thiazolidinediones favored)

Sulfonylureas Versus DPP-4 Inhibitors

One RCT compared glipizide (n=212) with sitagliptin (n=210).[107] The authors stated that there were no significant differences between treatments for outcomes of abdominal pain, diarrhea, and vomiting at 58 weeks, but that sitagliptin-treated participants had statistically

significantly less nausea ($P = 0.025$); the number or percent of individuals with nausea was not reported.

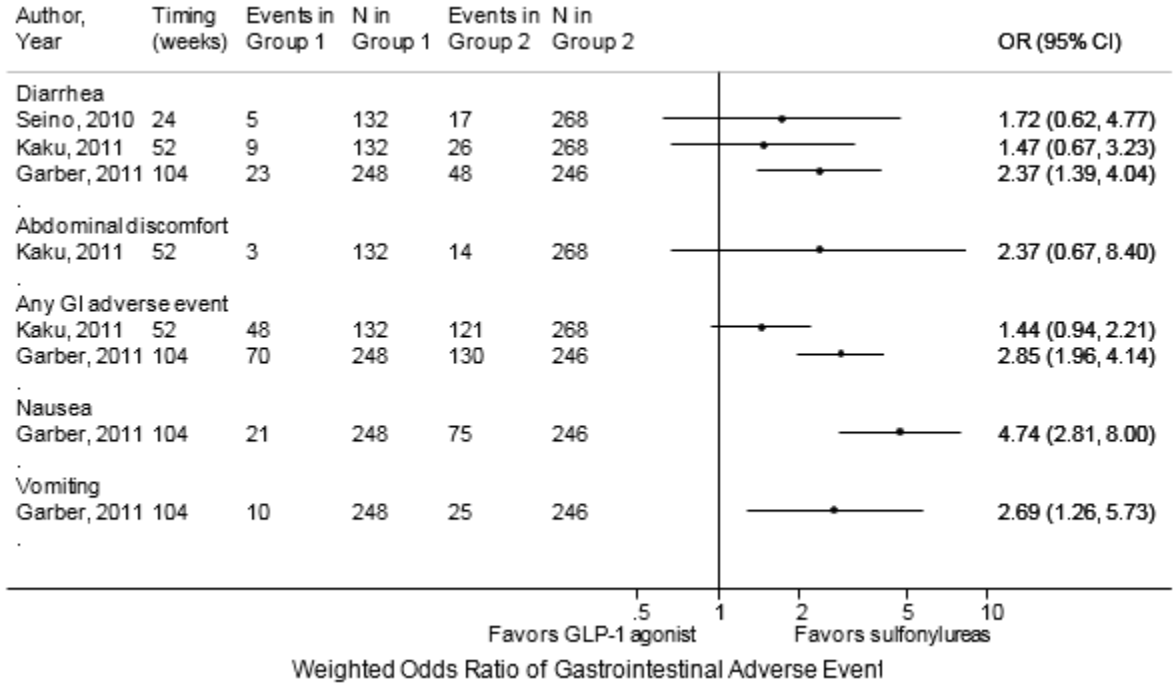
One RCT compared glimepiride with linagliptin.[106] By 34 weeks, 9 percent of individuals on each drug had an unspecified GI adverse event.

One trial was identified only in ClinicalTrials.gov (NCT01006603). A comparable number of GI adverse events occurred with glimepiride and with saxagliptin (19/359 versus 15/359 for diarrhea; 8/359 versus 4/359 for nausea). (SOE: Low; Neither favored)

Sulfonylureas Versus GLP-1 Receptor Agonists

Three RCTs compared GI adverse events between glibenclamide and liraglutide.[109, 110, 113] GI adverse events were more common with GLP-1 receptor agonists (range in RD 3% to 9% for studies lasting 52 weeks or less) (Figure 74). We did not pool any of these outcomes due to insufficient studies per outcome or differences in study duration for diarrhea. (SOE: Moderate; Sulfonylureas favored for diarrhea) (SOE: Low; Sulfonylureas favored for other GI adverse events)

Figure 74. Pooled odds ratio of gastrointestinal adverse events comparing sulfonylureas with GLP-1 receptor agonists



CI = confidence interval; GLP-1 = glucagon-like peptide-1; Group 1 = sulfonylureas; Group 2 = glucagon-like peptide-1 agonists; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

DPP-4 Inhibitors Versus GLP-1 Receptor Agonists

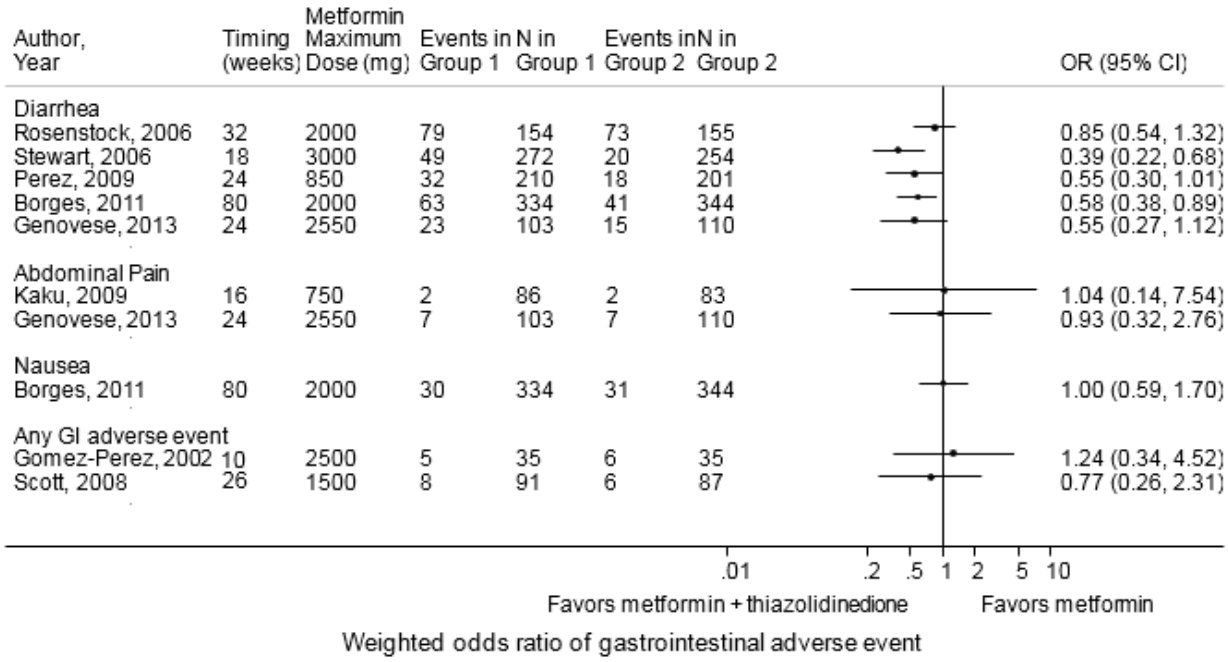
One RCT compared sitagliptin to exenatide.[73] At 26 weeks, there tended to be more diarrhea (5.5% vs 10.9%), dyspepsia (1.8% vs 7.3%), nausea (3.7% vs 11.3%), and vomiting (1.8% vs 4.8%) with exenatide than sitagliptin. (SOE: Low; DPP-4 inhibitors favored)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Ten RCTs compared metformin with a combination of metformin and a thiazolidinedione for the rates of GI adverse events. Diarrhea was more common among the metformin monotherapy group (OR, 0.59; 95% CI, 0.45 to 0.76; I-squared, 16.4%; five studies), with no consistent differences in other GI adverse events (Figure 75).[59, 67, 117-121, 125, 127, 247] Dosages of metformin were generally similar in both arms within trials, and differences in dosages between trials did not appear to impact the GI adverse events. (SOE: Low; Combination of metformin plus a thiazolidinedione favored for diarrhea; Neither favored for other GI-related outcomes)

Figure 75. Odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus a thiazolidinedione



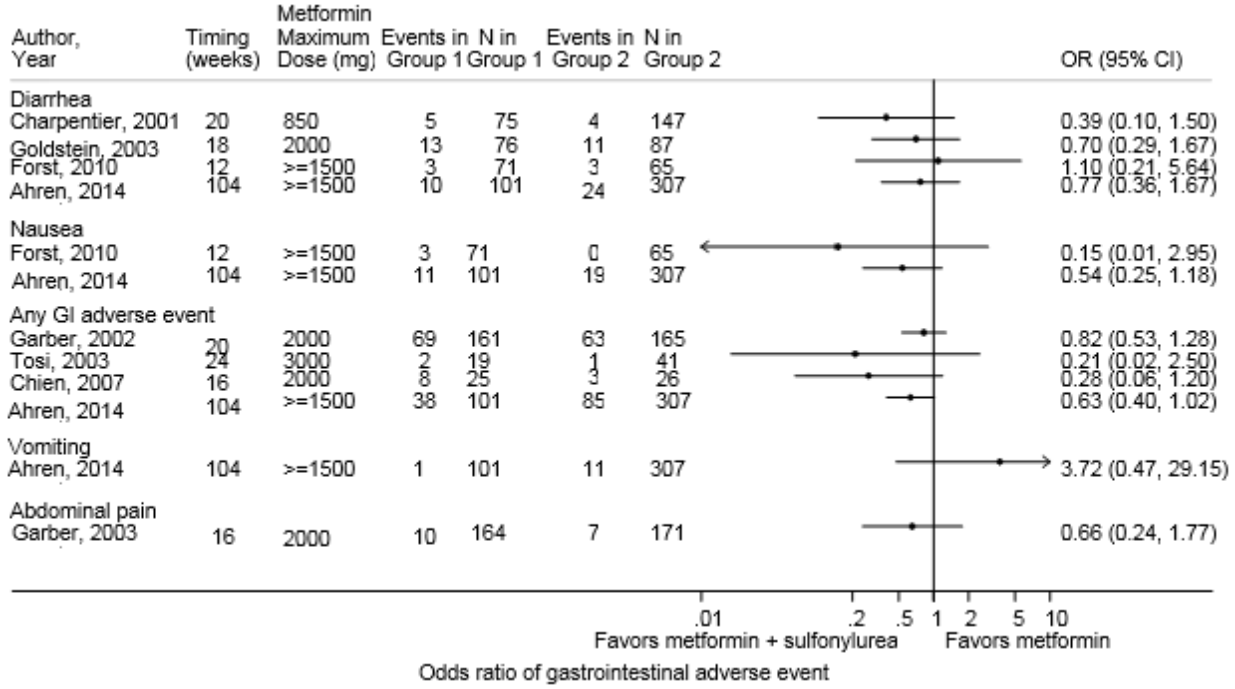
CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a thiazolidinedione; mg = milligrams; OR = odds ratio

Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

Twelve RCTs examined GI adverse events comparing metformin with metformin plus a sulfonylurea.[47, 129-131, 133, 134, 136-141] No clear differences in GI adverse events were identified between arms (Figure 76). For the outcome with at least three studies, there was a pooled OR of 0.66 (95% CI, 0.34 to 1.28; I-squared, 0%; three studies) for diarrhea. We did not combine the four studies reporting on any GI adverse event owing to differences in study duration and dosing differences. Two of the studies used lower doses of metformin with combination therapy compared with monotherapy.[47, 129] Studies that reported on combinations of adverse events that did not conform with the definition of "any" adverse event (diarrhea, nausea, vomiting or pain) are not included in the summary figure. (SOE: Low; Neither arm favored)

Figure 76. Odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus a sulfonylurea*



CI = confidence interval; GI = gastrointestinal; Group 1 = metformin; Group 2 = combination of metformin plus a sulfonylurea; mg = milligrams; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

*Studies with more than one dosing arm under the same gastrointestinal outcome are reported twice in the figure to demonstrate effects of different dosing arms.

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Three RCTs compared metformin with metformin plus alogliptin.[84, 154, 157] Five RCTs compared metformin with metformin plus linagliptin.[86, 139, 152, 155, 162] Six RCTs compared metformin and metformin plus saxagliptin.[87, 144, 146, 147, 151, 161] Twelve RCTs compared metformin and metformin plus sitagliptin.[85, 118, 141-143, 145, 148, 149, 153, 156, 159, 256]

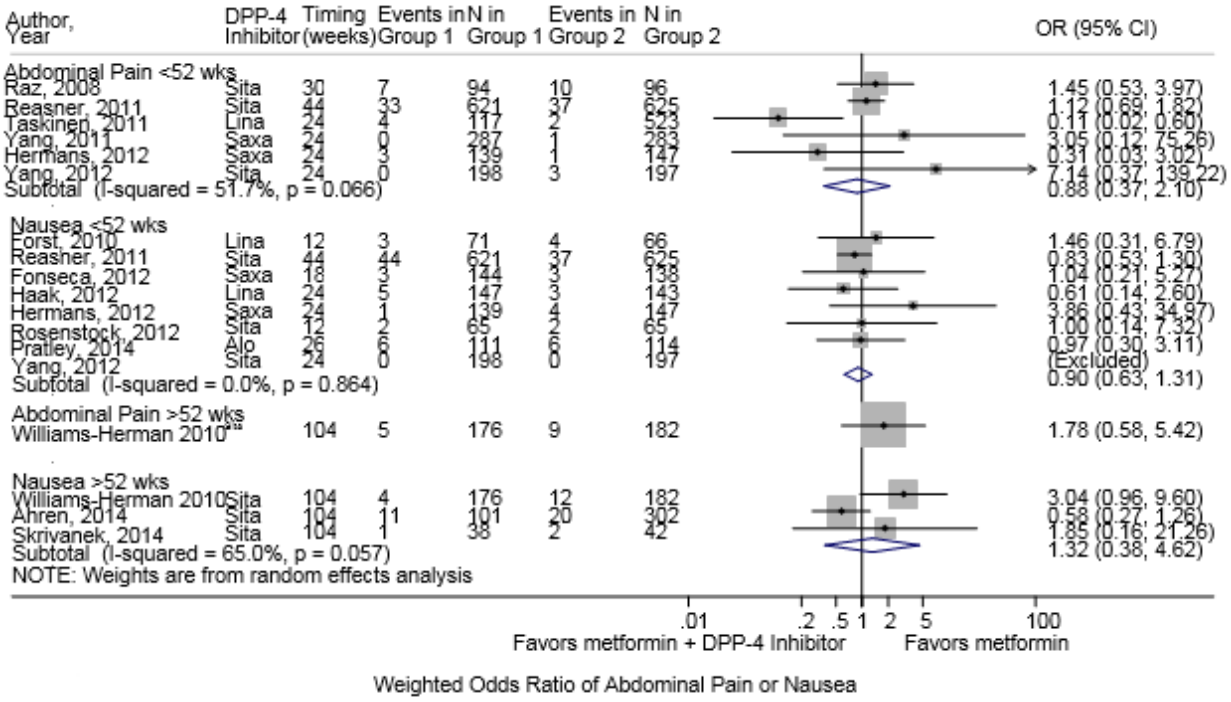
There were inconsistent findings for GI adverse events depending on the outcome examined. There were no between-group differences for abdominal pain, nausea, and any GI adverse event (Figure 77 and Figure 78). Diarrhea was more common in the metformin monotherapy arm in the shorter studies but may have been more common in the metformin plus DPP-4 inhibitor arms in the longer studies (Figure 79). Vomiting occurred less often with metformin monotherapy in the longer studies, and showed no differences between groups in studies lasting less than a year (Figure 80).

All the RCTs except for two[147, 162] had comparable dosing of metformin in the monotherapy and combination arms. The first study with dosing differences was included in the meta-analyses where appropriate since dosing differences were small between arms (1500 to 2000 mg metformin in the monotherapy and 1500 mg metformin in the combination arm) and unlikely to impact the findings.[147] Sensitivity analyses excluding this study confirmed that the study did not influence the results.[147] The second study[162] was excluded from the meta-analyses since the metformin monotherapy arm was at 2000 mg daily and the metformin dosing in the combination arm was only at 1000 mg daily, which could bias the study findings to favor the combination

arm. In this excluded study,[162] diarrhea occurred 16 percent of the time in the metformin monotherapy arm and 12 percent in the combination arm. These findings and other GI adverse events reported in this study[162] were consistent with the meta-analysis results for the comparably-dosed studies.

Two trials were identified solely in ClinicalTrials.gov (NCT00960076; NCT01076088). The former found less diarrhea with metformin monotherapy compared with metformin combined with saxagliptin (3.5% versus 5.8%). The other trial reported similar numbers of individuals with GI adverse events in the metformin monotherapy group (nine people reported diarrhea; 4 people reported nausea) and the metformin plus sitagliptin group (4 people reported diarrhea; 8 people reported nausea). (SOE for abdominal pain: Low; Neither favored for shorter and longer studies) (SOE for nausea: Moderate for shorter studies and low for longer studies; Neither favored) (SOE for any GI adverse event: Moderate for shorter studies and Low for longer studies; Neither favored) (SOE for diarrhea: Low; combination favored for shorter studies and metformin favored for longer studies) (SOE for vomiting: Low for longer studies; Metformin monotherapy favored and Moderate for shorter studies; neither favored)

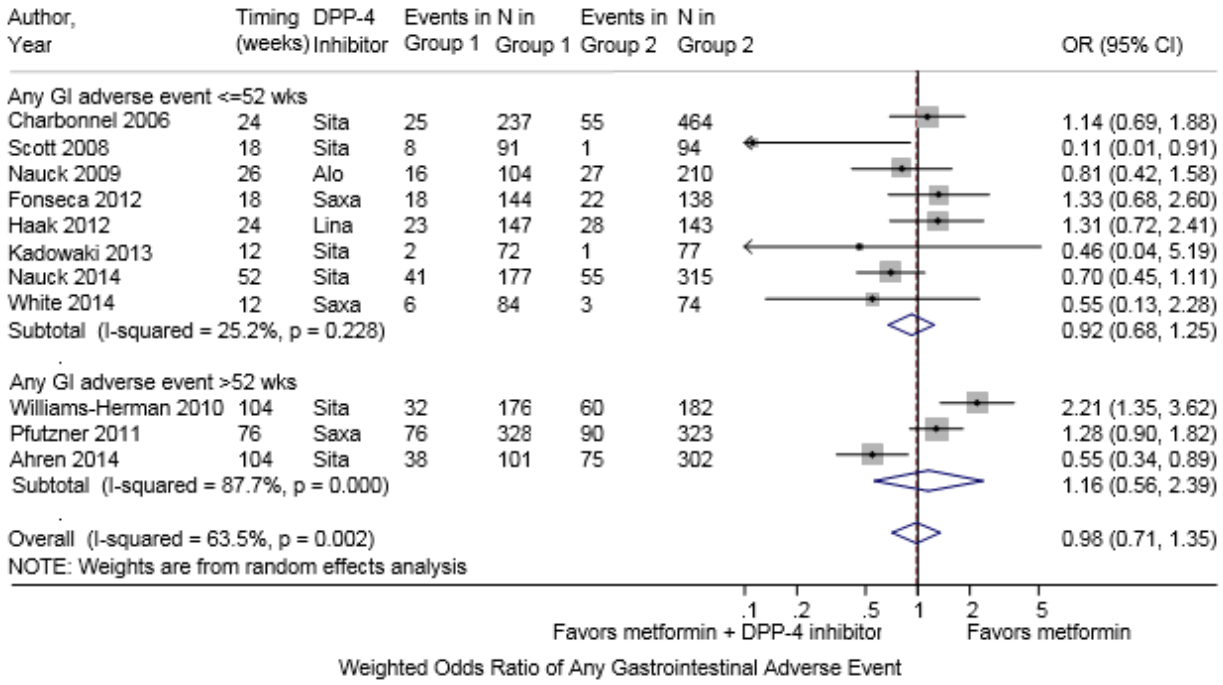
Figure 77. Pooled odds ratio of abdominal pain or nausea comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

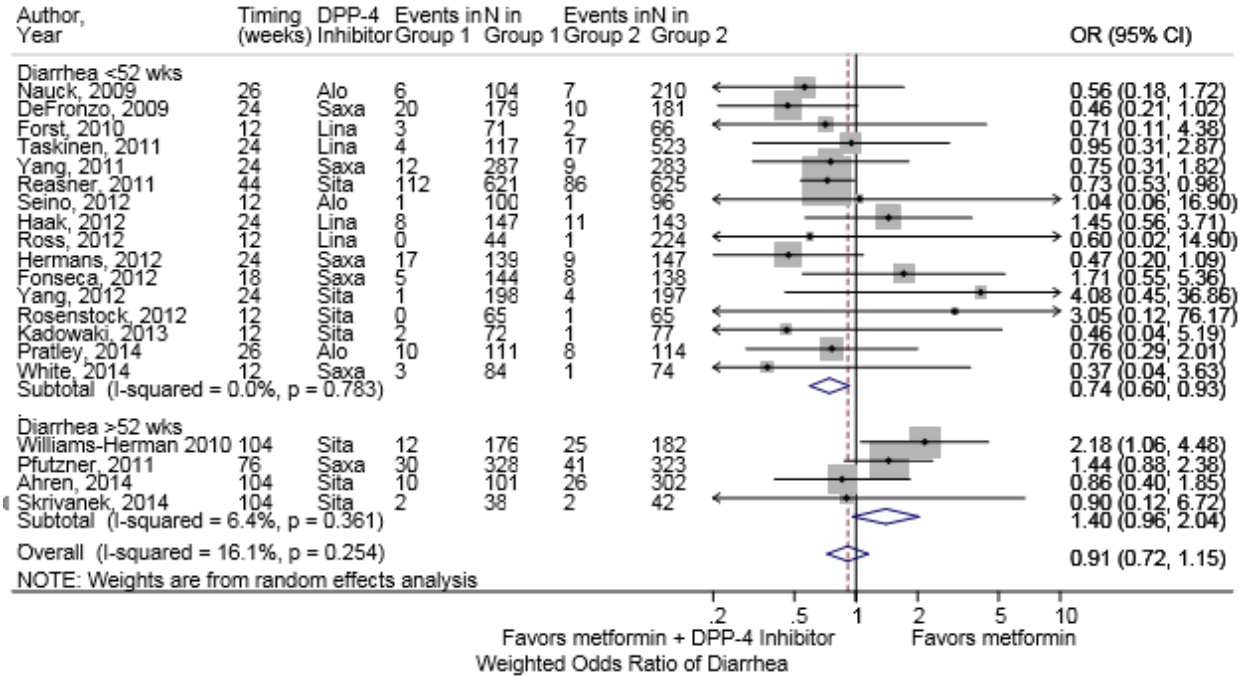
Figure 78. Pooled odds ratio of any gastrointestinal adverse event comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

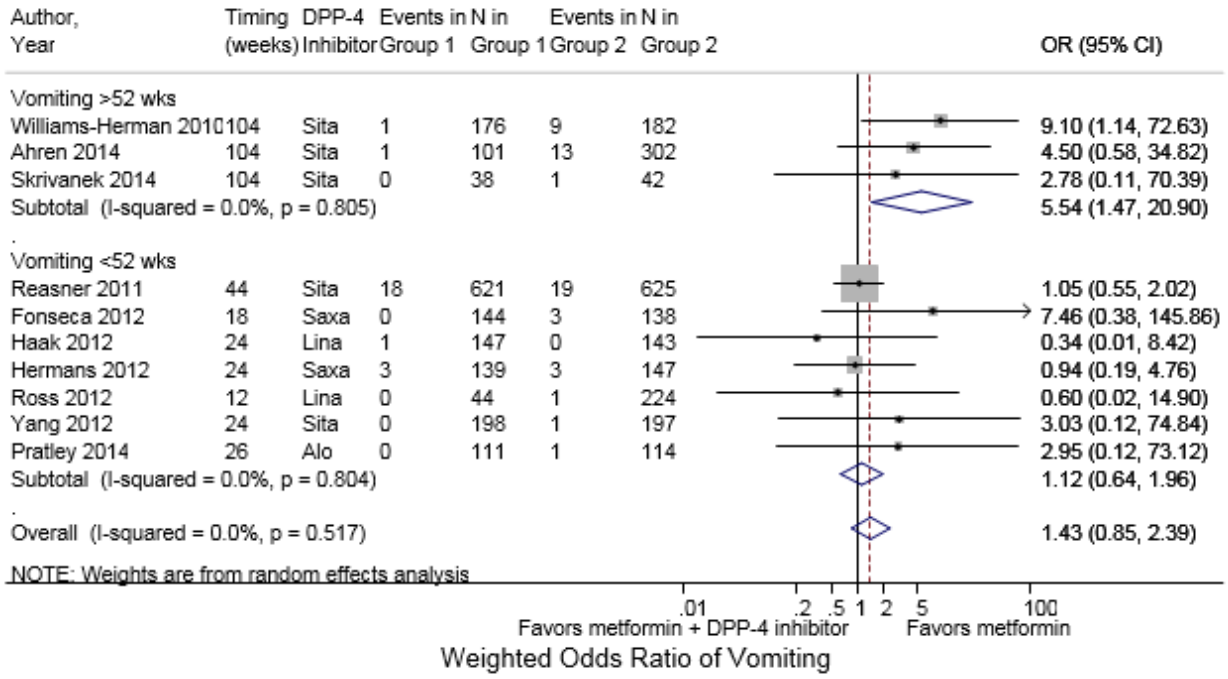
Figure 79. Pooled odds ratio of diarrhea comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Figure 80. Pooled odds ratio of vomiting comparing metformin with a combination of metformin plus a DPP-4 inhibitor

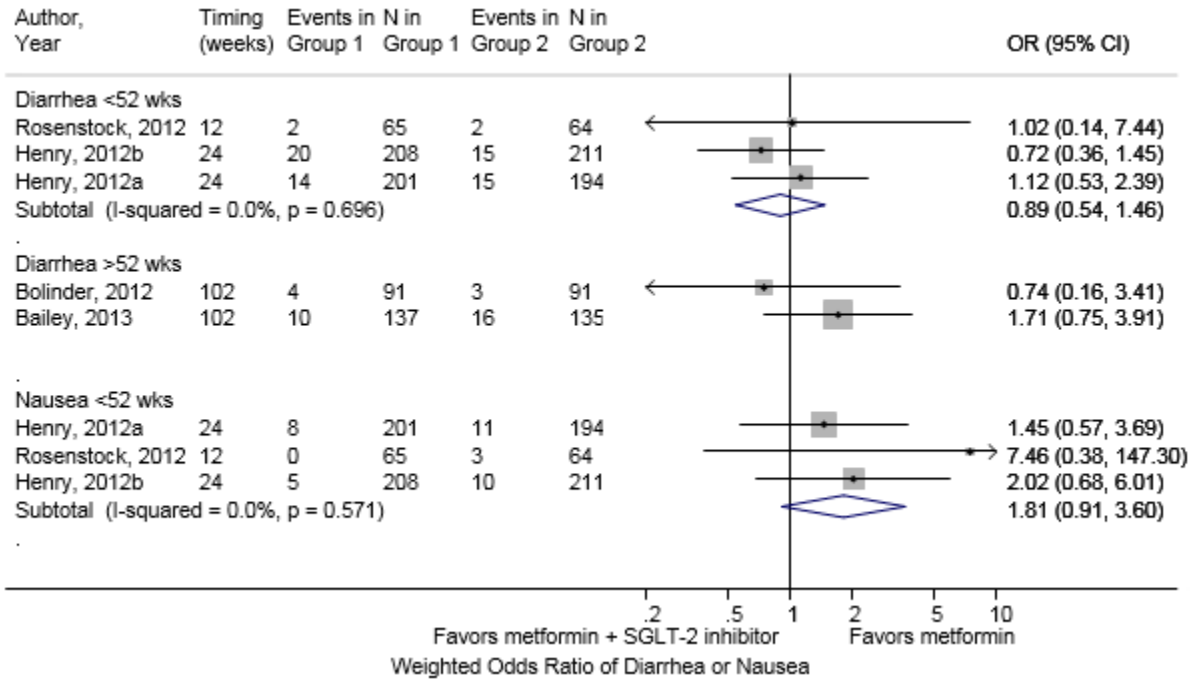


CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

One RCT compared metformin with metformin combined with canagliflozin for diarrhea and nausea.[156] Four RCTs (published in three articles) compared metformin to metformin combined with dapagliflozin for diarrhea and nausea.[88, 169, 170] One RCT compared metformin to metformin combined with empagliflozin for diarrhea and nausea.[153] There were no consistent differences in diarrhea between arms. Nausea tended to be more common with combination therapy, although the finding was not statistically significant (Figure 81). (SOE: Moderate; Neither favored for diarrhea) (SOE: Low; metformin favored for nausea)

Figure 81. Pooled odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus an SGLT-2 inhibitor



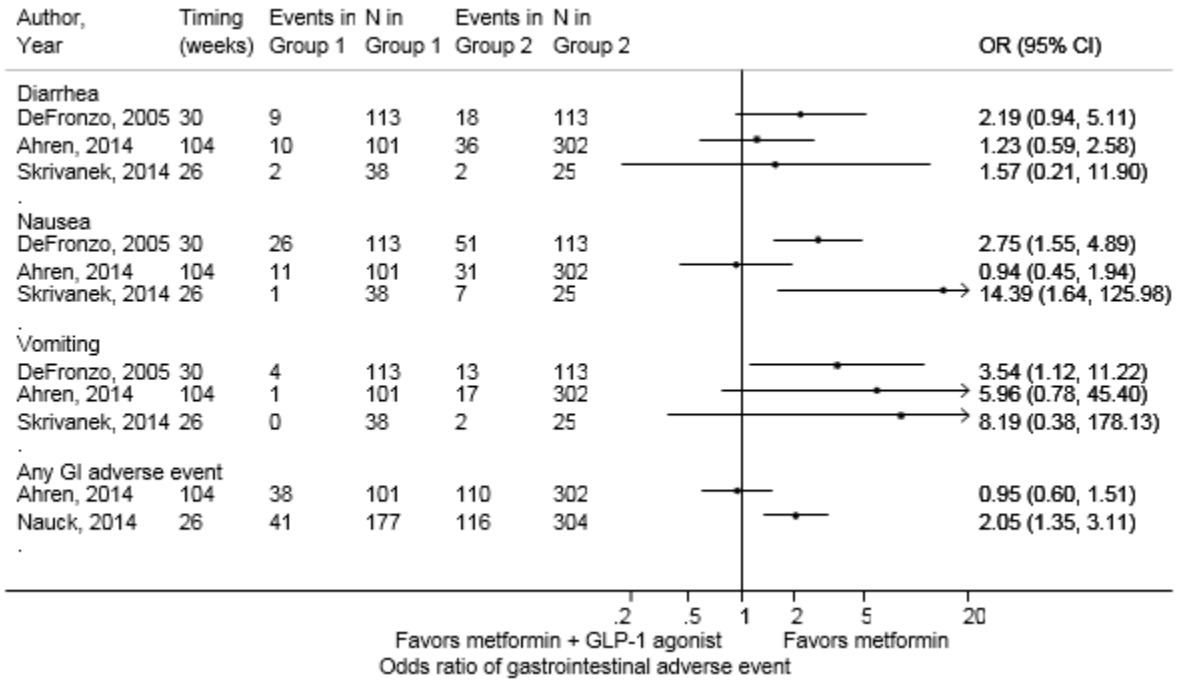
CI = confidence interval; Group 1 = metformin; Group 2 = metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Metformin Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Four RCTs compared metformin with metformin plus a GLP-1 receptor agonist.[141, 159, 174, 256] Metformin plus a GLP-1 receptor agonist showed no clear between-group differences in GI adverse events compared with metformin alone in one study,[256] but there were more GI adverse events in the combination arm in the other studies (Figure 82).[141, 159, 174] We did not pool data in meta-analyses due to insufficient numbers of studies and due to differences in study duration. (SOE: Low; Neither favored)

Figure 82. Odds ratio of gastrointestinal adverse events comparing metformin with a combination of metformin plus a GLP-1 receptor agonist



CI = confidence interval; GLP-1 = glucagon-like peptide-1; Group 1 = metformin; Group 2 = metformin plus a glucagon-like peptide-1 agonist; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Five RCTs compared GI adverse events in the combination of metformin plus a thiazolidinedione versus metformin plus a sulfonylurea, with little between-group difference (Table 75). The RD between-groups ranged from -5.0% to 2.1%.[175, 178, 180, 181, 265] (SOE: Moderate; Neither favored)

Table 75. Randomized controlled trials comparing a combination of metformin plus a thiazolidinedione with a combination of metformin plus a sulfonylurea on gastrointestinal adverse events

Author, Year	Outcome	Event Rates (Metformin Plus Thiazolidinedione Versus Metformin Plus Sulfonylurea)
Derosa, 2005[265]	Flatulence	4.2% (2/48) versus 2.1% (1/47)
Garber, 2006[180]	Combined GI events Diarrhea Abdominal pain	10% (16/155) versus 11% (18/159) 3% (5/155) versus 6% (10/159) 4% (6/155) versus 6% (10/159)
Umpierrez, 2006[178]	Diarrhea	4.7% (5/104) versus 6% (6/96) (no difference)
Hamann, 2008[175]	Combined GI events	13% (38/294) versus 18% (54/301)
Maffioli, 2013[181]	Withdrawal owing to nausea	1% (1/86) versus 1% (1/84)

GI = gastrointestinal

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Three RCTs compared GI adverse events in the combination of metformin plus pioglitazone or rosiglitazone versus the combination of metformin plus sitagliptin with mixed results.[118, 187, 188] Diarrhea and nausea tended to be more common with sitagliptin in one trial,[188] but there was only one occurrence of each (4%) in the sitagliptin group (and none reported in the pioglitazone group) in the other trial.[187] In the third trial, six of 87 patients in the metformin plus rosiglitazone arm and one of 94 patients in the metformin plus sitagliptin arm experienced a GI adverse event, a difference that was close to statistically significant.[118] (SOE: Low; Neither favored)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

One RCT compared diarrhea, nausea, and vomiting in the combination of metformin plus pioglitazone versus the combination of metformin plus exenatide at 26 weeks.[188] There was more diarrhea (7% versus 18%), nausea (5% versus 24%), and vomiting (3% versus 11%) in the group receiving exenatide; all differences are statistically significant. The range in ORs was 2.9 to 6.3, and range in RDs were 8% to 19%. (SOE: Moderate; Combination of metformin plus a thiazolidinedione favored)

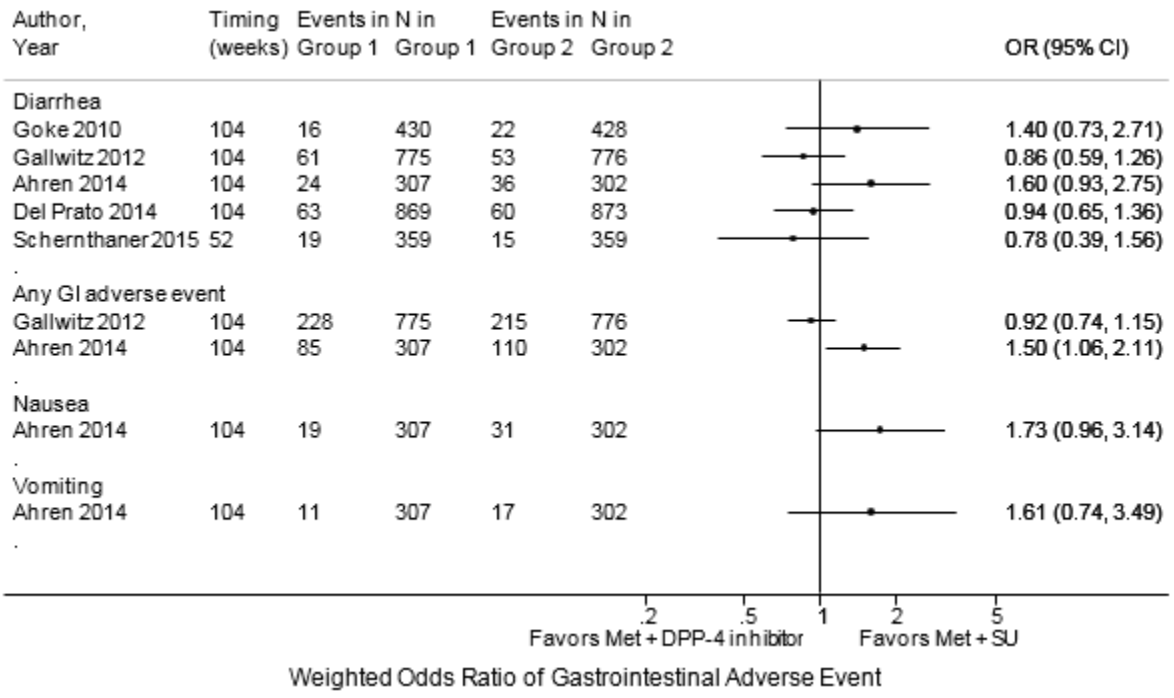
Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Seven RCTs compared diarrhea, abdominal pain, nausea, vomiting, and unspecified GI adverse events in the combination of metformin plus glipizide or glimepiride versus metformin plus alogliptin, linagliptin, sitagliptin, or saxagliptin, with no difference between treatments (Figure 83).[139, 141, 192-195, 197] The OR for the four trials with similar study duration of 104 weeks for diarrhea was 0.97 (95% CI, 0.76 to 1.24; I-squared, 0 percent).[141, 194, 195, 197] No single study strongly influenced the results, and no substantial heterogeneity was identified.

One trial was identified in ClinicalTrials.gov (NCT00856284) that randomized 869 people to metformin plus 5 mg of glipizide and 378 people to metformin plus 25 mg of alogliptin. Metformin plus alogliptin had more GI adverse events (32 nausea, 1 severe vomiting, 60

diarrhea) than metformin plus glipizide (20 nausea and 63 diarrhea). No severe diarrhea was described in either group. (SOE: High; Neither favored)

Figure 83. Odds ratio of gastrointestinal adverse events comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = a combination of metformin plus a sulfonylurea; Group 2 = a combination of metformin plus a dipeptidyl peptidase-4 inhibitor; Met = metformin; OR = odds ratio; SU = sulfonylurea
Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Three RCTs compared metformin plus glipizide or glimepiride with metformin plus dapagliflozin or empagliflozin on the outcomes of diarrhea and nausea.[54, 199, 200] There was little difference between treatments. A meta-analysis was not performed because the trials reported adverse events at 1, 2, and 4 years after randomization.

One trial identified from ClinicalTrials.gov (NCT01368081) reported no significant difference in the number of individuals with diarrhea with metformin plus sulfonylurea (5 of 63) and metformin plus empagliflozin (4 of 65). (SOE: Low; Neither favored)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Three RCTs compared metformin plus glibenclamide or glimepiride with metformin plus albiglutide or exenatide for diarrhea, nausea, or vomiting, with a similar and low incidence of adverse events in one trial of exenatide (diarrhea: 1/65 versus 2/63; vomiting: 1/65 versus 1/63),[205] but a greater percentage of individuals with GI adverse events with exenatide in another trial (diarrhea: 7% versus 12%; nausea: 2% versus 29%; vomiting: 2% versus 9%).[53] Diarrhea and nausea were more common with albiglutide (diarrhea: 11.9% versus 8.6%; nausea: 8.9%

versus 5.2%; vomiting: 5.6% versus 3.6%; unspecified adverse events: 36.4% versus 37.6%).[141] A meta-analysis was not performed because the trials differed in duration. (SOE: Low; Combination of metformin plus a sulfonylurea favored)

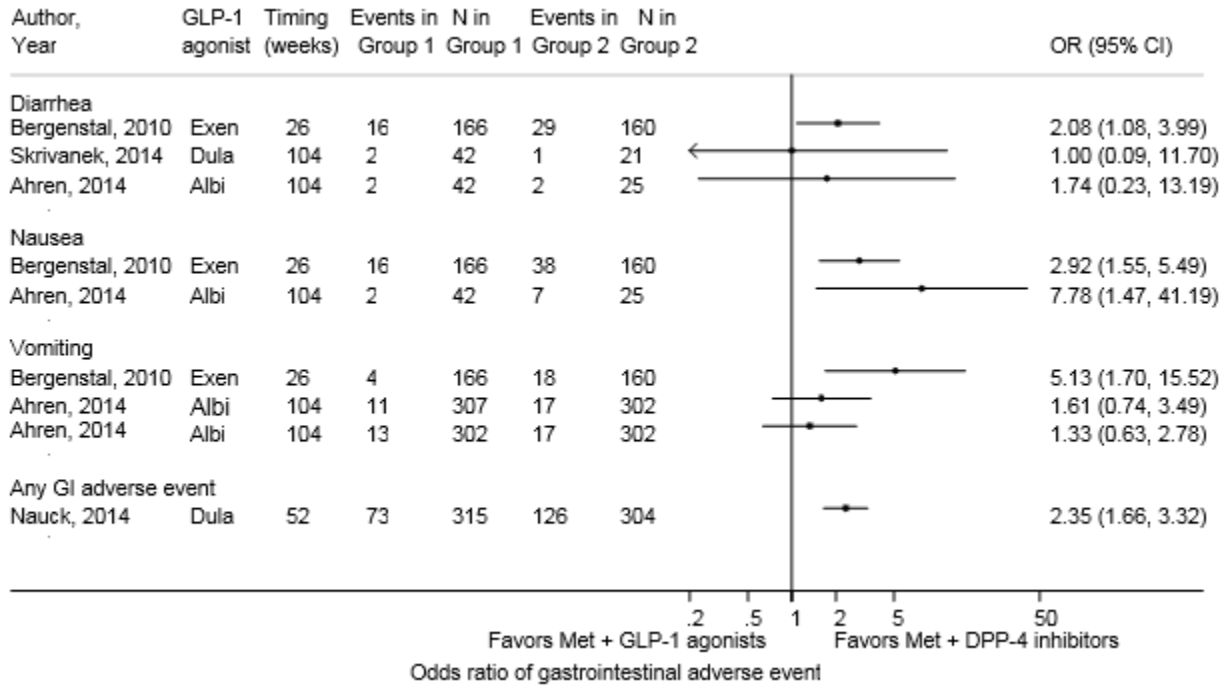
Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Two trials compared metformin plus sitagliptin with metformin plus different doses of canagliflozin or empagliflozin.[153, 156] Diarrhea and nausea were reported for the canagliflozin comparisons, and dyspepsia was reported for the empagliflozin comparisons. There were no clear differences in GI side effects for either medication. (SOE: Low; Neither favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Four trials reported on GI adverse events comparing metformin plus sitagliptin with metformin plus albiglutide, dulaglutide, or exenatide.[141, 159, 188, 256] There were more GI adverse events with GLP-1 receptor agonists in three of the four trials, with a range in RD of 0% to 23% (Figure 84). (SOE: Moderate; Combination of metformin plus a DPP-4 inhibitor favored)

Figure 84. Odds ratio of gastrointestinal adverse events comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 receptor agonist



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Group 1 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; Group 2 = combination of metformin plus a glucagon-like peptide-1 agonist; Met = metformin; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Combination of Metformin Plus a GLP-1 Receptor Agonist Versus a Combination of Metformin Plus a Premixed Insulin

One trial compared metformin plus exenatide with metformin plus insulin aspart 70/30 at 26 weeks for diarrhea, dyspepsia, nausea, and vomiting.[213] There was no difference in diarrhea between the treatments (11% versus 8%). Differences between groups for the other outcomes could not be evaluated because they were only reported for exenatide (6% dyspepsia; 19% nausea; 10% vomiting). (SOE: Insufficient)

Combination of Metformin Plus a Basal Insulin Versus a Combination of Metformin Plus a Premixed Insulin

One RCT compared metformin in a combination regimen with either insulin glargine or lispro for diarrhea; neither arm was favored.[214]

One trial was reported only in ClinicalTrials.gov (NCT01068652). Thirteen of 200 people who received metformin plus insulin detemir had diarrhea compared with 15 of 203 people in the metformin plus biphasic insulin aspart 30 group. (SOE: Low; Neither favored)

Strength of Evidence for Gastrointestinal Side Effects

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 76, Table 77, and Table 78 and summarized in the key points. All studies were RCTs. Study limitations for most comparisons in the strength of evidence table were graded as low or medium; only two comparisons were graded as having high study limitations owing to lack of description of randomization or blinding or failure to describe withdrawals or dropouts. In general, we did not find strong relative differences in outcomes by study quality. We did not find any evidence of publication bias comparing results published in peer-reviewed journals to results published on ClinicalTrials.gov. However, for the comparison of thiazolidinediones with GLP-1 receptor agonists, an additional trial was found in ClinicalTrials.gov with consistent findings to the two published studies favoring thiazolidinediones. This study would likely increase the strength of evidence from low to moderate. We considered GI side effects a direct outcome, because they were measured directly from patient report. The most common reasons for downgrading the evidence were imprecision, inconsistency, and study limitations.

Table 76. Strength of evidence domains for monotherapy comparisons in terms of gastrointestinal side effects among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. TZD	8 (6,250)	Medium	Consistent	Direct	Precise	Undetected	Moderate	TZD favored for diarrhea, 0.24 (0.17 to 0.34) and nausea
Metformin vs. SU	12 (6094)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	SU favored for diarrhea, 0.42 (0.24 to 0.72); abdominal pain, 0.44 (0.29 to 0.67); nausea and vomiting, 0.45 (0.31 to 0.65); and any GI adverse events, 0.45 (0.28 to 0.72)
Metformin vs. DPP-4 inhibitors	6 (5,842)	Low	Consistent	Direct	Precise	Undetected	High	DPP-4 inhibitors favored for nausea, 0.37 (0.15 to 0.91) and diarrhea, 0.38 (0.18 to 0.83)
Metformin vs. SGLT-2 inhibitors	4 (2,041)	Medium	Consistent	Direct	Imprecise	Undetected	Low	SGLT-2 inhibitors favored for diarrhea and nausea
Metformin vs. GLP-1 receptor agonists	3 (879)	Low	Inconsistent	Direct	Imprecise for diarrhea; Precise for nausea/ vomiting	Undetected	Low for diarrhea; Moderate for nausea/ vomiting	GLP-1 receptor agonists favored for diarrhea; Metformin favored for nausea/vomiting, 1.73 (1.01 to 2.95)
TZD vs. SU	5 (6,432)	Low	Consistent	Direct	Precise	Undetected	High	Neither favored; range in OR, 0.8 to 2.0; range in RD, -1.2% to 1.7%
TZD vs. DPP-4 inhibitors	2 (1,031)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
TZD vs. GLP-1 receptor agonists	2 (1,236)	Low	Consistent	Direct	Imprecise	Undetected‡	Low	TZD favored
SU vs. DPP-4 inhibitors	2 (653)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored

Table 76. Strength of evidence domains for monotherapy comparisons in terms of gastrointestinal side effects among adults with type 2 diabetes (continued)

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
SU vs. GLP-1 receptor agonists	3 (1,568)	High	Consistent	Direct	Precise for diarrhea; Imprecise for all other GI adverse events	Undetected	Moderate for diarrhea; Low for abdominal pain, any GI adverse event, nausea and vomiting	SU favored; range in OR for diarrhea, 1.5 to 2.4; range in RD for diarrhea, 3% to 9%
DPP-4 inhibitors vs. GLP-1 receptor agonists	1 (820)	Low	Not applicable	Direct	Not evaluated	Undetected	Low	DPP-4 inhibitors favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; OR = odds ratio; RD = risk difference; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

‡ An additional article was found in clinical trials.gov which was consistent with the two other studies favoring thiazolidinediones over GLP-1 receptor agonists. Inclusion of this study may have increased our strength of evidence from low to moderate.

Table 77. Strength of evidence domains for metformin versus metformin combination comparisons in terms of gastrointestinal side effects among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + TZD	10 (3,878)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin + TZD favored for diarrhea; Neither favored for other GI-related outcomes
Metformin vs. metformin + SU	12 (4,317)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither drug favored for diarrhea or any GI adverse events
Metformin vs. metformin + DPP-4 inhibitors	26 (14,324)	Low	Consistent for nausea, any GI adverse event, and vomiting; Inconsistent for all others	Direct	Precise for nausea, any GI adverse event, and vomiting for shorter studies; Imprecise for all others	Undetected	Moderate for any GI adverse event, nausea, and vomiting (shorter studies) Low for abdominal pain, diarrhea, and vomiting (longer studies)	Neither favored for shorter studies; 0.9 (0.6 to 1.3) for nausea; 0.9 (0.7 to 1.3) for any GI adverse event; 1.1 (0.6 to 2.0) for vomiting; and for abdominal pain For diarrhea, the combination was favored in the shorter studies and metformin monotherapy was favored in the longer studies For vomiting in the longer studies, metformin monotherapy was favored
Metformin vs. metformin + SGLT-2 inhibitors	6 (2,918)	Low	Consistent	Direct	Precise	Undetected	Moderate for diarrhea; Low for nausea	Neither favored for diarrhea, 0.9 (0.5 to 1.5), Metformin favored for nausea
Metformin vs. metformin + GLP-1 receptor agonists	4 (2,713)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Table 78. Strength of evidence domains for metformin-based combination comparisons in terms of gastrointestinal side effects among adults with type 2 diabetes

Comparison	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary[†]
Metformin + TZD vs. metformin + SU	5 (1,382)	Low	Consistent	Direct	Precise	Undetected	Moderate	Neither favored; range in OR, 0.5 to 2.0; range in RD, -5% to 2.1%
Metformin + TZD vs. metformin + DPP-4 inhibitors	3 (747)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + TZD vs. metformin + GLP-1 receptor agonists	1 (514)	Low	Not applicable	Direct	Imprecise	Undetected	Moderate	Metformin + TZD favored; range in OR, 2.9 to 6.3; range in RD, 8% to 19%
Metformin + SU vs. metformin + DPP-4 inhibitors (long-term studies)	7 (8,321)	Low	Consistent	Direct	Precise	Undetected	High	Neither favored for diarrhea at 104 weeks; 1.0 (0.8 to 1.2)
Metformin + SU vs. metformin + SGLT-2 inhibitors	3 (3,177)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + SU vs. metformin + GLP-1 receptor agonists	3 (2,018)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Metformin + SU favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	2 (946)	Medium	Not applicable	Direct	Not evaluated	Undetected	Low	No difference
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 receptor agonists	4 (2,891)	Medium	Consistent	Direct	Precise	Undetected	Moderate	Metformin + DPP-4 inhibitors favored; range in OR, 1.0 to 5.1; range in RD, 0% to 23%
Metformin + GLP-1 receptor agonists vs. metformin + premixed insulin	1 (363)	High	Not applicable	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + basal insulin vs. metformin + premixed insulin	1 (317)	Medium	Not applicable	Direct	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; OR = odds ratio; RD = risk difference; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack

of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.
† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Cancer

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

A single retrospective cohort study, from the England Cancer Registry, reported no difference in non-melanoma cancer risk for thiazolidinediones users (N=31,372) versus metformin users (N=109,708) (adjusted RR, 0.96; 95% CI, 0.81 to 1.13, *P* not reported) over 4 years of followup.[255] (Not graded)

Metformin Versus Sulfonylureas

Four retrospective, cohort studies compared cancer outcomes for metformin and sulfonylurea users (Table 79).[225, 254, 255, 266] Three studies reported no difference between metformin and sulfonylurea users.[225, 255, 266] The other study only provided results stratified by statin use, indicating a possible interaction with statin use.[254] (SOE: Low; Neither favored for long-term cancer risk)

Table 79. Retrospective cohort studies comparing metformin with sulfonylureas on cancer

Author, Year	Population	Followup	Outcome	Results
van Staa, 2012[255]	England Cancer Registry [n=68,209 (sulfonylurea); n=109,708 (metformin)]	4-5 years	Non-melanoma cancer	HR 1.03; 95% CI, 0.91 to 1.17 Reference=metformin
Andersson, 2010[225]	Danish Patient Registry Patients with heart failure (N=5,852)	10 years	Death from cancer	HR 1.01; 95% CI, 0.72 to 1.43 Reference=sulfonylurea
Lehman, 2012[254]	Veterans Health Administration [n=533 (metformin-statin); n=2404 (sulfonylurea-statin); n=175 (metformin-no statin); n=1,930 (sulfonylurea-no statin)]	270.4 weeks	Incident prostate cancer	Statin users HR 0.69; 95% CI, 0.5 to 0.92, *P* = 0.01 Reference=sulfonylurea Non users of statins HR 2.15; 95% CI, 1.83 to 2.52, *P* < 0.0001 Reference=sulfonylurea
Kowall, 2015[266]	German Disease Analyzer (IMS Health) – primary care clinics (N=22,556)	4.8 years	Incident cancer by ICD-10 code	Adjusted HR, 1.09; 95% CI, 0.87 to 1.36 Reference=metformin

CI = confidence interval; HR = hazard ratio; ICD-10 = International Classification of Diseases

Metformin Versus DPP-4 Inhibitors

Two RCTs of metformin plus placebo (N=510) versus a DPP-4 inhibitor plus placebo (N=514) evaluated cancer outcomes.[85, 87] Each study reported one cancer event: one death due to pancreatic neoplasm/sepsis[87] and one occurrence of esophageal cancer,[85] in the metformin arms. Neither study reported on cancer in the DPP-4 inhibitor arm.[85, 87] Followup ranged from 76[87] to 104 weeks.[85] (SOE: Insufficient)

Metformin Versus SGLT-2 Inhibitors

A single RCT (N=404) of metformin plus placebo versus dapagliflozin plus placebo, with 24 weeks of followup, reported on occurrence of cancer.[88] The RCT reported no bladder cancer in either arm and a single case of breast cancer in the SGLT-2 arm; breast cancer was not reported on in the metformin arm.[88] (SOE: Insufficient)

Thiazolidinediones Versus Sulfonylureas

A 56-week, multi-center trial in the US, including Puerto Rico, reported two events of stage IV colon cancer (2/251, 0.8%) in the sulfonylurea arm and none in the thiazolidinedione arm (0/251, 0.0%).[95] (SOE: Low; Thiazolidinediones favored)

Sulfonylureas Versus DPP-4 Inhibitors

Two short-term RCTs compared sulfonylurea with DPP-4 inhibitor monotherapy and reported on cancer outcomes collected through passive ascertainment.[106, 107] One 52-week RCT reported one case of colon cancer in the glimepiride arm (1/76, 1.3%) and did not report on cancer in the linagliptin arm (NR/151).[106] The other RCT compared glipizide with sitagliptin among participants with at least moderate renal insufficiency and reported five cases of cancer in the sitagliptin arm (5/210, 2.3%) and none in the sulfonylurea arm (0/212, 0.0%), over 58 weeks of followup.[107] In that study, cancer cases were chronic myeloid leukemia in a participant with baseline leukocytosis, breast cancer diagnosed after 4 days of sitagliptin initiation, lung cancer in a participant with 40 pack-years of smoking, a pancreatic mass, and a case of polycythemia vera in a participant with a germline JAK-2 mutation.[107] (SOE: Insufficient)

Sulfonylureas Versus GLP-1 Receptor Agonists

One RCT compared glimepiride with liraglutide and reported on cancer outcomes with 104 weeks of followup but did not report if ascertainment was active.[113] Two cases of breast cancer occurred in the liraglutide 1.8 mg arm (2/251, 0.8%) and two cases of thyroid tumors (one benign thyroid neoplasm and one papillary thyroid cancer) in the liraglutide 1.2 mg arm (1/247, 0.4%); cancer outcomes were not reported on in the sulfonylurea arm (N=248).[113] These events were only reported if they were considered to be possibly related to the trial drug.[113] (SOE: Insufficient)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

A single RCT compared metformin (N=101) with metformin plus glimepiride (N=307) and reported no cases of thyroid cancer in either arm at 104 weeks.[141] Of note, withdrawal rates were greater than 30 percent across arms, and the investigators did not use an intention-to-treat analysis. (SOE: Insufficient)

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Nine RCTs compared metformin with metformin plus a DPP-4 inhibitor.[85, 87, 105, 141, 142, 154, 159, 160, 162] We did not combine these studies in a meta-analysis because of lack of consistent ascertainment of and reporting on cancer outcomes; and, when reported, heterogeneous definitions of cancer outcomes (Table 80). Two studies had long-term follow up (104 weeks).[85, 141] Of these, the RCT with active ascertainment reported two cases of thyroid cancer in the

metformin plus DPP-4 inhibitor arm (0.7%) and none in the metformin arm (0.0%) at 104 weeks.[141] Results were mixed across the other studies, with many arms not reporting on cancer outcomes. (SOE: Insufficient)

Table 80. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on cancer

Author, Year	Followup (Weeks)	Outcome	Active/Passive Ascertainment	Metformin Events/N (%)	Metformin + DPP-4 Inhibitor Events/N (%)
Ji, 2015[162]	14	Pancreatic cancer	NR	0/345	Linagliptin 5 mg: 0/344 (0)
Wang, 2015[160]	24	Gastric cancer	NR	0/100 (0)	1/205 (0.5)
		Pancreatic cancer	NR	0/100 (0)	0/205 (0)
Nauck, 2009[154]	26	Discontinuation because of prostate cancer	Passive	NR/104	Alogliptin 12.5 mg: 1/213 (0.5) Alogliptin 25 mg: NR/210
		Discontinuation because of endometrial cancer	Passive	NR/104	Alogliptin 12.5 mg: 1/213 (0.5) Alogliptin 25 mg: NR/210
Nauck, 2014[159]*	26	Thyroid cancer	NR	0/177 (0)	0/315 (0)
Raz, 2008[142]	30	Cases of cancer	Active	3/94 (3)	0/96 (0)
Xu, 2015[105]	48	Cholangiocarcinoma	NR	0/136 (0)	1/142 (0.7)
Pfutzner, 2011[87]	76	Death due to pancreatic neoplasm/sepsis	NR	1/328 (0.3)	Saxagliptin 5 mg: NR/320 Saxagliptin 10 mg: NR/323
Ahren, 2014[141]	104	Thyroid cancer	Active	0/101 (0)	2/302 (0.7)
Williams-Herman, 2010[85]	104	Esophageal cancer	NR	Metformin 1000 mg: 1/182 (0.5) Metformin 2000 mg: NR/182	Metformin 2000 mg + sitagliptin 100 mg: NR/182 Metformin 1000 mg + sitagliptin 100 mg: NR/190

DPP-4 = dipeptidyl peptidase-4; mg = milligram; NR = not reported
*Cancer outcome at 52 weeks not reported in the metformin arm and none reported in the MET+DPP-4 arm

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Four RCTs compared metformin with metformin plus an SGLT-2 inhibitor and reported on cancer outcomes (Table 81).[88, 165, 169, 170] Reporting of cancer was incomplete for many studies, and studies did not report on whether there was active ascertainment for cancer outcomes. Therefore, we did not perform a meta-analysis for this comparison (Table 81). Cancer outcomes were rare but appeared to occur at similar rates in the treatment arms; most studies were small and less than 1 year in duration. (SOE: Low; Neither favored)

Table 81. Randomized controlled trials comparing metformin with a combination of metformin plus a SGLT-2 inhibitor on cancer

Author, Year	Followup (Weeks)	Outcome	Active/Passive Ascertainment	Metformin Events/N (%)	Metformin + SGLT-2 Inhibitor Events/N (%)
Qiu, 2014[165]	18	Colon cancer	NR	NR/93	Canagliflozin 100 mg: NR/93 Canagliflozin 300 mg: 1/93 (1.1)
Henry, 2012[88]	24	Bladder malignancy	NR	0/201 (0)	0/194 (0)
Bolinder, 2012[169]	50	Prostatic cancer or prostatic adenoma	NR	1/91 (1.1)	1/91 (1.1)
		Basal cell carcinoma	NR	1/91 (1.1)	NR/91
		Breast cancer leading to discontinuation	NR	0/91 (0)	1/91 (1.1)
Bailey, 2013[170]	102	Unspecified adverse event (lung cancer)	NR	1/137 (0.7)	Dapagliflozin 2.5 mg: NR/137 Dapagliflozin 5 mg: 1/137 (0.7) (bladder cancer) Dapagliflozin 10 mg: 1/135 (0.7) (breast cancer)

mg = milligram; NR = not reported; SGLT-2 = sodium-glucose co-transporter-2

Metformin Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Two RCTs compared metformin with metformin plus a GLP-1 receptor agonist and reported on cancer outcomes.[141, 159] One trial did active surveillance for thyroid cancer and reported one case of follicular thyroid cancer in the metformin plus albiglutide arm (1/302, 0.3%) and no cases (0/101, 0.0%) in the metformin arm at 104 weeks.[141] The 52-week RCT reported no cases of thyroid cancer in the metformin plus dulaglutide arms (metformin plus dulaglutide 0.75 mg/week, n=302; metformin plus dulaglutide 1.5 mg/week, n=304) and did not report on thyroid cancer in the metformin arm (n=177).[159] (SOE: Low; Metformin favored)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

One 24-week RCT compared the combination of moderately-dosed metformin plus pioglitazone with the combination of moderately-dosed metformin plus glimepiride and reported on cancer outcomes, but whether ascertainment was active was not reported.[185] A single case of prostate cancer occurred in the metformin plus glimepiride arm (1/142, 0.7%), and cancer was not reported on in the metformin plus pioglitazone arm (n=146).[185] More than 20 percent of participants withdrew from each arm.[185] (SOE: Insufficient)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a DPP-4 Inhibitor

A single 26-week RCT compared the combination of metformin plus pioglitazone with the combination of metformin plus sitagliptin and reported on cancer outcomes; the method of ascertainment was not described.[188] A single case of papillary thyroid cancer occurred in the metformin plus sitagliptin arm (1/166, 0.6%), and no events were reported in the metformin plus pioglitazone arm (0/165, 0.0%).[188] More participants withdrew from the metformin plus pioglitazone arm (21%) than the metformin plus sitagliptin arm, and the investigators did not use an intention-to-treat analysis for this outcome.[188] (SOE: Insufficient)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

A single 26-week RCT compared the combination of metformin plus pioglitazone with the combination of metformin plus weekly exenatide and reported on cancer outcomes; the method of ascertainment was not described.[188] No cases of thyroid cancer were reported in either arm (metformin plus pioglitazone: 0/165, 0.0% and metformin plus exenatide: 0/160, 0.0%).[188] (SOE: Insufficient)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Three RCTs, with 104 weeks of followup, compared the combination of metformin plus a sulfonylurea with the combination of metformin plus a DPP-4 inhibitor and reported on cancer outcomes (Table 82).[141, 194, 195] Cancer incidence was slightly higher in the metformin plus DPP-4 arms than the metformin plus sulfonylurea arms, in these 2-year trials. More than 20 percent of participants withdrew from these studies. Two of the studies used an intention-to-treat analysis.[194, 195] An additional RCT with only 52 weeks of followup also reported a higher incidence of cancer in metformin plus DPP-4 inhibitor arm than in the metformin plus a sulfonylurea.[193] (SOE: Low; Combination of metformin plus a sulfonylurea favored)

Table 82. Randomized controlled trials comparing a combination of metformin with a sulfonylurea with a combination of metformin plus a DPP-4 inhibitor on cancer

Author, Year	Followup (Weeks)	Outcome	Active/Passive Ascertainment	ITT Analysis	Metformin + SU Events/N (%)	Metformin + DPP-4 Inhibitor Events/N (%)
Ahren, 2014[141]	104	Thyroid cancer	Active	No	0/307 (0.0%)	2/302 (0.7%)
Gallwitz, 2012[194]	104	Prostate, breast, and colon cancer*	NR	Yes	7/775 (0.9%)	10/776 (1.3%)
Goke, 2010[195]	104	Acute myeloid leukemia	NR	Yes	NR/430	1/428 (0.2%)
Schernthaner, 2015[193]	52	Neoplasm	NR	No	3/360 (0.8)	10/360 (2.8%)

DPP-4 = dipeptidyl peptidase-4; ITT = intention-to-treat; NR = not reported; SU = sulfonylurea
* Unclear if ascertained for specific types of cancer

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

Two RCTs compared the combination of metformin plus an sulfonylurea with the combination of metformin plus an SGLT-2 inhibitor and reported on cancer outcomes.[199, 201] In one 104-week trial using passive ascertainment, the authors reported more cases of cancer (prostate cancer, n=3; breast cancer, n=1; gastric cancer, n=1; and pancreatic cancer, n=2) in the metformin plus dapagliflozin arm (7/406, 1.7%) than in the metformin plus glipizide arm (prostate cancer, basal cell skin cancer, and lung cancer; 3/408, 0.7%).[199] In the other RCT (also with 104 weeks of followup), a single death due to cervical cancer was reported in the metformin plus sulfonylurea arm; the study did not report on this outcome for the metformin plus SGLT-2 inhibitor arms.[201] (SOE: Insufficient)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

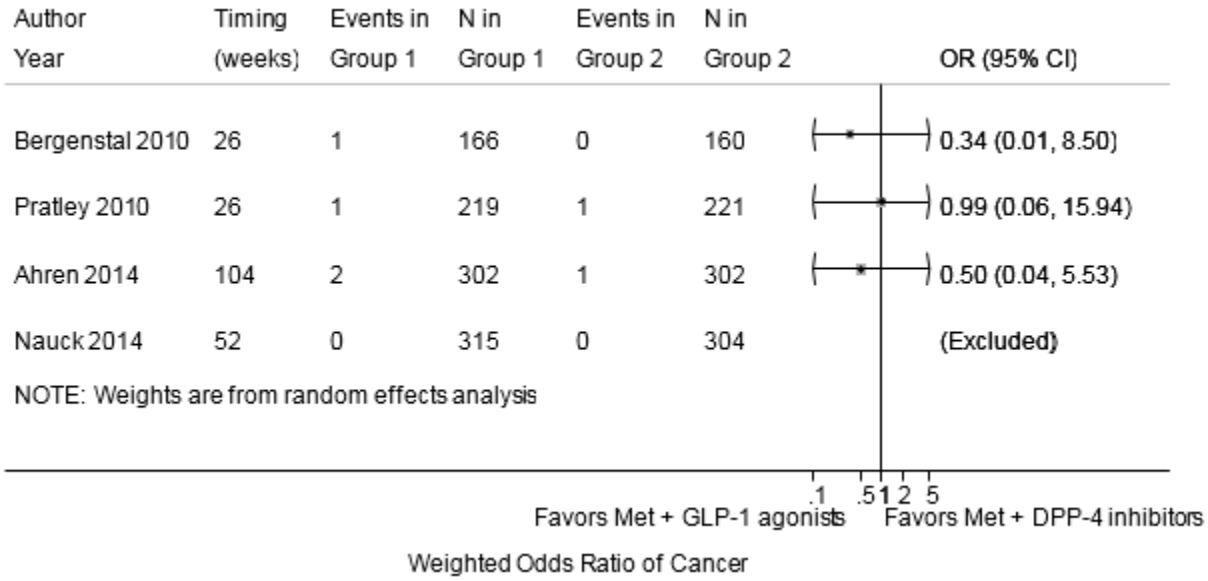
Two RCTs compared the combination of metformin plus glimepiride with the combination of metformin plus a GLP-1 receptor agonist and reported on cancer outcomes.[53, 141] Both trials reported thyroid cancer events in the metformin plus GLP-1 receptor agonist arm.[53, 141] In the study by Ahren 2014, the investigators actively ascertained for thyroid cancer with 104 weeks of followup and found no thyroid cancer in the metformin plus glimepiride arm (0/307, 0.0%) and one case in the metformin plus albiglutide arm (1/302, 0.3%).[141] In the other trial (maximum followup of 3 years), which did not report on the method of ascertainment of cancer outcomes, the authors reported three cases of thyroid cancer (3/511, 0.6%) in the metformin plus exenatide arm and did not report on thyroid cancer for the metformin plus sulfonylurea arm. In that trial, the authors also reported a single case of breast cancer in the metformin plus sulfonylurea arm (1/508, 0.2%) and did not report on breast cancer for the metformin plus exenatide arm.[53] (SOE: Low; Combination of metformin plus a sulfonylurea favored for long-term risk of thyroid cancer)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Three short-term RCTs[159, 188, 210] and one long-term RCT compared the combination of metformin plus a GLP-1 receptor agonist with the combination of metformin plus a DPP-4 inhibitor and found conflicting results on risk of thyroid cancer (Figure 85). None of the short-term studies reported active ascertainment of thyroid cancer, and one did not provide results for the intention-to-treat population.[188] The long-term RCT (104 weeks) actively ascertained thyroid cancer and reported two events in the metformin plus DPP-4 arm and one event in the metformin plus GLP-1 receptor agonist arm; the authors did not evaluate this outcome in the intention-to-treat population.[141]

Withdrawal rates were high across the study arms (range, 13% to 77%) with most arms having more than 30 percent losses to followup.[141, 159, 188, 210] (SOE: Low; Combination of metformin plus a GLP-1 receptor agonist favored)

Figure 85. Pooled odds ratio of cancer events comparing the combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus a GLP-1 receptor agonist



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a Basal Insulin

A single 25-week RCT compared the combination of metformin plus sitagliptin with the combination of metformin plus insulin glargine and reported two cases of cancer (Kaposi's sarcoma and prostate cancer) in the metformin plus sitagliptin arm (2/264, 0.8%) and none in the metformin plus insulin glargine arm (0/237, 0.0%).[211] (SOE: Low; Combination of metformin plus a basal insulin favored)

Strength of Evidence for Cancer

We found low or insufficient strength of evidence on cancer outcomes for all comparisons of interest, as described in the Key Points and Table 83, Table 84, and Table 85.

The major limitation of the evidence on cancer for the diabetes medication comparisons was the lack of studies. For RCTs, major study limitations included high rates of withdrawals (>20%) combined with lack of an intention-to-treat approach and lack of active ascertainment of, or reporting on, cancer outcomes. We usually could not determine consistency because of a lack of studies (i.e., one study available for a given comparison), or evidence was graded as inconsistent based on only a few studies for each comparison. The evidence on all comparisons was imprecise because of insufficient sample size for cancer outcomes.

We identified several unpublished studies that may have affected our grading of the evidence. For the comparison of sulfonylurea monotherapy and DPP-4 inhibitor monotherapy, two unpublished studies favored sulfonylurea monotherapy. These results could have moved our evidence grade from "insufficient" to "low" for this comparison and suggested that sulfonylurea monotherapy is favored over DPP-4 inhibitors. Also, addition of an unpublished study with long-

term followup of the published study comparing metformin to metformin plus a sulfonylurea would have led to the conclusion that metformin is favored over the combination of metformin plus a sulfonylurea, although with low strength of evidence. The same unpublished study also provided additional results for the comparison of metformin to combination therapy with metformin and a DPP-4 inhibitor and to the combination of metformin plus a GLP-1 receptor agonist; results suggested that metformin was favored over both combination therapies. These would also have been conclusions based on low strength of evidence for both comparisons. Two unpublished studies with long-term follow up supported the published evidence that the combination of metformin plus a sulfonylurea is favored over the combination of metformin plus a DPP-4 inhibitor.

We found two additional unpublished studies of comparisons for which there were no published studies: thiazolidinedione vs. DPP-4 inhibitors and metformin plus basal insulin vs. metformin plus premixed insulin.

Finally, most evidence for the comparisons of interest included studies that did not report on cancer events in all arms. While this limited our ability to synthesize data quantitatively, we do not believe that this was a source of selective analysis reporting bias, as much as a reflection of a lack of a focus on active ascertainment and reporting of cancer outcomes.

Table 83. Strength of evidence domains for monotherapy comparisons and cancer outcomes among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. SU	Observational: 4 (211,367)	Medium	Consistent	Direct	Imprecise	NA	Low	Neither favored
Metformin vs. DPP-4 inhibitors	RCTs: 2 (1,014)	Low	Consistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. SGLT-2 inhibitors	RCT: 1 (404)	Medium	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
TZD vs. SU	RCT: 1 (502)	Medium	Unknown	Direct	Imprecise	Undetected	Low	TZD favored
SU vs. DPP-4 inhibitors	RCTs: 2 (653)	Low	Inconsistent	Direct	Imprecise	Suspected	Insufficient	Unable to determine
SU vs. GLP-1 receptor agonists	RCT: 1 (746)	Medium	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; NA = not applicable; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating the outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Table 84. Strength of evidence domains for metformin versus metformin-based combination comparisons and cancer outcomes among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + SU	RCT: 1 (1049)	High	Unknown	Direct	Imprecise	Suspected	Insufficient	Unable to determine
Metformin vs. metformin + DPP-4 inhibitors	RCTs: 8 (6266)	Low	Inconsistent	Direct	Imprecise	Suspected	Insufficient	Unable to determine 4 RCTs did not report on events in all arms
Metformin vs. metformin + SGLT-2 inhibitors	RCTs: 4 (1610)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + GLP-1 receptor agonists	RCTs: 2 (2147)	High	Inconsistent	Direct	Imprecise	Suspected	Low	Metformin favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; NA = not applicable; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating the outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Table 85. Strength of evidence domains for combination therapy comparisons and cancer among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + pio vs. metformin + SU	RCT: 1 (305)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + pio vs. metformin + DPP-4 inhibitors	RCT: 1 (514)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + pio vs. metformin + GLP-1 receptor agonists	RCT: 1 (514)	High	Unknown	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + SU vs. metformin + DPP-4 inhibitors (long-term studies)	RCTs: 4 (4,179)	Medium	Consistent	Direct	Imprecise	Suspected	Low	Metformin + SU favored for longer-term cancer risk
Metformin + SU vs. metformin + SGLT-2 inhibitors (long-term studies)	RCT: 2 (2264)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + SU vs. metformin + GLP-1 receptor agonists (long-term studies)	RCT: 2 (2,078)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin + SU favored for long-term thyroid cancer risk
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 receptor agonists	RCT: 4 (3,107)	High	Consistent	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 receptor agonists favored
Metformin + DPP-4 inhibitor vs. metformin + basal insulin	RCT: 1 (515)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin + basal insulin favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; pio = pioglitazone; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating the outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Congestive Heart Failure

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Three RCTs[50, 70, 76] and two observational studies[233, 243] examined heart failure for the comparison of metformin versus thiazolidinediones (Table 86). We did not conduct a meta-analysis because of differences in study duration and design. The two RCTs, each lasting less than 1 year, showed no events of heart failure in either arm.[70, 76] The third RCT, the ADOPT study,[50] had over 1,400 subjects in each arm with a median duration of treatment of 4 years. In this study, the investigators compared metformin with rosiglitazone on the primary outcome of time to monotherapy failure. While the study was not powered to detect differences in cardiovascular events and excluded patients with heart failure at baseline, there was no statistically significant difference between the incidence of investigator-reported heart failure in these two arms (22/1456 for rosiglitazone versus 19/1454 for metformin).[50]

Two observational studies with 6 to 8 years of followup also compared metformin with thiazolidinediones.[233, 243] Both studies reported point estimates suggesting harm from thiazolidinediones compared with metformin; the results were only close to statistically significant for the comparison of pioglitazone versus metformin in one of the two studies (Table 86).[233] (SOE: Low; Metformin favored)

Table 86. Studies comparing metformin with thiazolidinediones on congestive heart failure

Author, Year	Study Design	Comparison	Heart Failure Incidence (Metformin as Reference Group)
Kahn, 2006[50]	RCT	Rosiglitazone versus metformin	22/1456 versus 19/1454 versus; OR, 1.2 (95% CI, 0.6 to 2.3)
Erem, 2014[70]	RCT	Pioglitazone versus metformin	0/19 versus 0/19
Esposito, 2011[76]	RCT	Pioglitazone versus metformin	0/55 versus 0/55
Pantalone, 2009[233]	Observational study	Rosiglitazone versus Metformin	HR, 1.16 (95% CI, 0.78 to 1.73)
		Pioglitazone versus metformin	HR, 1.38 (95% CI, 1.00 to 1.90)
Hsiao, 2009[243]	Observational study	Rosiglitazone versus metformin	HR, 1.30 (95% CI, 0.89 to 1.89)
		Pioglitazone versus metformin	HR, 1.54 (95% CI, 0.65 to 3.64)

CI = confidence interval; HR = hazard ratio for thiazolidinediones with metformin as reference group; OR = odds ratio; RCT = randomized controlled trial

Metformin Versus Sulfonylureas

Two studies (one RCT and one observational study) reported on the risk of heart failure events with metformin compared with the sulfonylureas, with both point estimates favoring metformin over sulfonylureas (Table 87).[231, 233] The 144-week RCT compared metformin with glipizide in adults with diabetes and a history of coronary artery disease, and reported a small, non-significant, greater number of events in the glipizide arm (10/148) compared to the metformin arm (9/156).[231] Rescue therapy was insulin and was initiated in about 20 percent of each arm. The larger retrospective observational study (N=20,450) compared metformin with

sulfonylurea in patients within one health care system in the United States from 1998 to 2006.[233] After adjusting for differences in baseline patient characteristics (e.g., gender, race, age, smoking status, and medications), sulfonylureas were associated with a greater risk of heart failure than metformin.[233] (SOE: Low; Metformin favored)

Table 87. Studies comparing metformin with sulfonylureas on congestive heart failure

Author, Year	Study Design	Comparison	Heart Failure Incidence (Sulfonylurea as Reference Group)
Hong, 2013[231]	RCT	Metformin versus glipizide	HR, 0.82 (95% CI, 0.31 to 2.13)
Pantalone, 2009[233]	Observational study	Metformin versus sulfonylurea (unspecified drug type)	HR, 0.76 (95% CI, 0.64 to 0.91)

CI = confidence interval; HR = hazard ratio for metformin with sulfonylureas as the reference group; RCT = randomized controlled trial

Metformin Versus DPP-4 Inhibitors

One RCT, lasting 26 weeks, compared metformin with alogliptin, with no heart failure events in either arm.[84] (SOE: Low; Neither favored)

Thiazolidinediones Versus Sulfonylureas

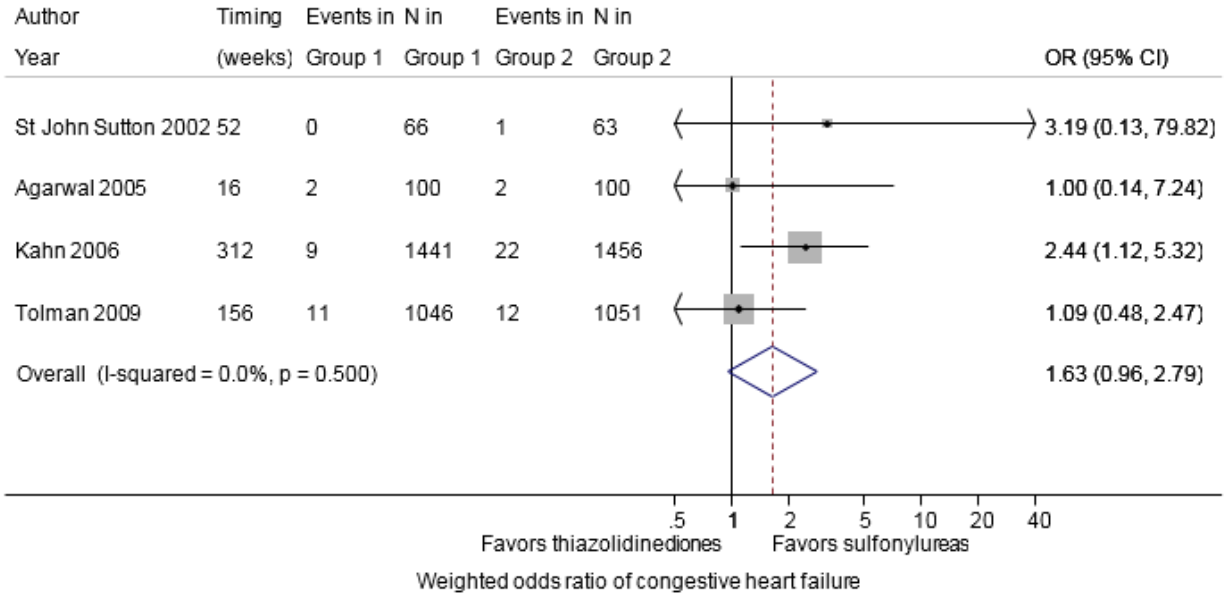
Four trials[49, 50, 52, 217] and two observational studies[233, 243] examined heart failure outcomes for the comparison of thiazolidinediones versus sulfonylureas (Table 88), finding no clear between-group differences. A meta-analysis of the four RCTs[49, 50, 52, 217] showed an increased risk of congestive heart failure with thiazolidinediones compared with sulfonylureas, which did not reach statistical significance (pooled OR, 1.62; 95% CI, 0.95 to 2.76) (Figure 86). There was no evidence of statistical heterogeneity among the included studies ($I^2 = 0\%$). Consistent with the meta-analysis of the RCTs, the two observational studies also showed increased risk of heart failure which did not reach statistical significance in three of the four thiazolidinedione arms compared with the sulfonylurea arms.[233, 243] (SOE: Low; Sulfonylureas favored)

Table 88. Observational studies comparing thiazolidinediones with sulfonylureas on congestive heart failure

Author, Year	Study Design	Comparison	Heart Failure Incidence (Sulfonylurea as Reference Group)
Pantalone, 2009[233]	Observational study	Rosiglitazone versus sulfonylurea	HR, 0.88 (95% CI, 0.60 to 1.31), p = 0.55
		Pioglitazone versus sulfonylurea	HR, 1.05 (95% CI, 0.77 to 1.43), p = 0.76
Hsiao, 2009[243]	Observational study	Rosiglitazone versus sulfonylurea	HR, 1.22 (95% CI, 0.86 to 1.74), p = 0.26
		Pioglitazone versus sulfonylurea	HR, 1.37 (95% CI, 0.58 to 3.20), p = 0.46

CI = confidence interval; HR = hazard ratio

Figure 86. Pooled odds ratio of congestive heart failure events comparing thiazolidinediones with sulfonylureas



CI = confidence interval; Group 1 = sulfonylureas; Group 2 = thiazolidinediones; OR = odds ratio
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Thiazolidinediones Versus DPP-4 Inhibitors

One 26-week RCT compared pioglitazone with alogliptin, reporting no heart failure events in either arm.[104] (SOE: Low; Neither drug favored)

Sulfonylureas Versus DPP-4 Inhibitors

One 58-week RCT comparing glipizide with sitagliptin reported four of 212 patients having heart failure events in the glipizide arm compared with none of 210 patients in the sitagliptin arm.[107] The only rescue therapy was insulin, which was initiated in about 10 percent of participants in each arm. (SOE: Insufficient)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Thiazolidinedione

Three RCTs, lasting from 26 to 80 weeks, compared metformin alone with the combination of metformin plus a thiazolidinedione, showing a small, non-significant, greater number of heart failure events in the metformin plus thiazolidinedione arms in two of the three studies (Table 89).[116, 126, 127] (SOE: Low; Metformin favored)

Table 89. Randomized controlled trials comparing metformin with a combination of metformin plus a thiazolidinedione on congestive heart failure

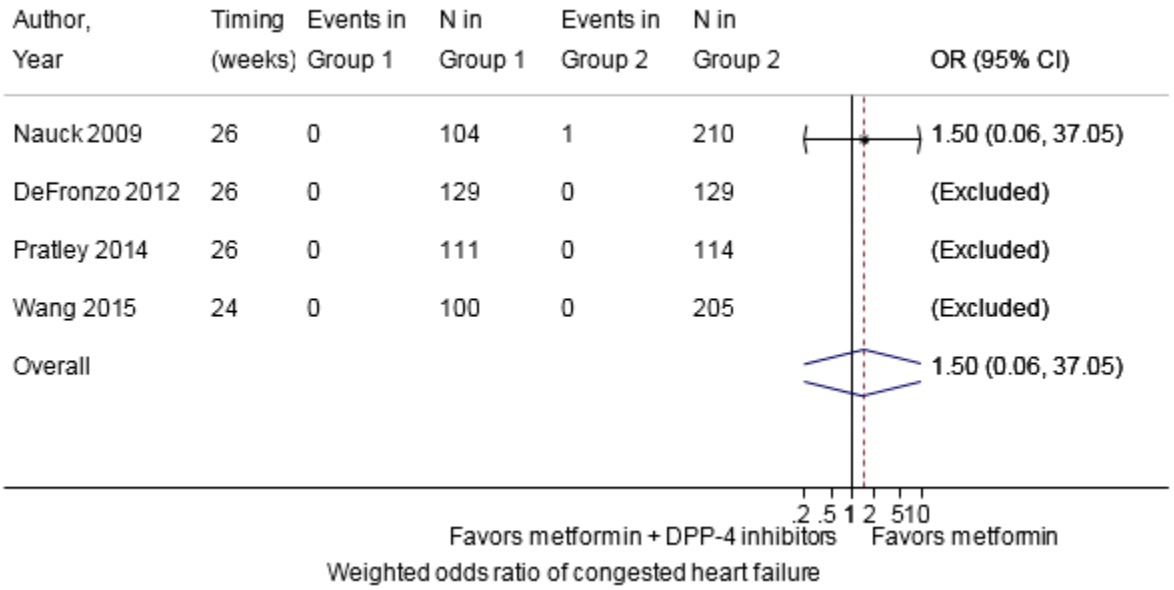
Author, Year	Study Design	Comparison	Heart Failure Incidence
Leiter, 2005[116]	RCT	Metformin versus metformin plus rosiglitazone	0/78 versus 0/158
Borges, 2011[127]	RCT	Metformin versus metformin plus rosiglitazone	0/334 versus 1/344
DeFronzo, 2012[126]	RCT	Metformin versus metformin plus pioglitazone	NR/129 versus 1/129

RCT = randomized controlled trial

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Four 26-week RCTs lasting 24 to 26 weeks compared metformin alone with the combination of metformin plus a DPP-4 inhibitor, showing no significant increased risk of heart failure in either arm.[84, 126, 154, 160] Two RCTs reported no events in either arm.[84, 160] One RCT reported no events in the combination arm but did not report on events in the metformin monotherapy arm.[126] The third RCT reported one event in the combination arm and did not report on events in the metformin monotherapy arm.[154] We combined these four RCTs in a meta-analysis, using zero events for the arms where no data were reported, and found no significant increased risk of heart failure between groups (pooled OR, 1.5; 95% CI, 0.06 to 37) (Figure 87).[84, 126, 154, 160] (SOE: Low; Neither favored)

Figure 87. Pooled odds ratio of congestive heart failure events comparing metformin with a combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin; Group 2 = combination of metformin plus a dipeptidyl peptidase-4 inhibitor; OR = odds ratio

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

One 24-week RCT comparing metformin plus pioglitazone with metformin plus glipizide reported two of 146 patients with heart failure events in the metformin plus pioglitazone arm and did not report whether there were any events in the 142 patients in the metformin plus glipizide arm.[185] (SOE: Insufficient)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a DPP-4 Inhibitor

One 26-week RCT comparing different doses of metformin plus pioglitazone with different doses of metformin plus alogliptin reported two heart failure events in the 258 patients in the metformin plus pioglitazone arms and did not report on heart failure events in the metformin plus alogliptin arms.[126] (SOE: Insufficient)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

One double-blind moderately-sized 52-week RCT compared fixed dose metformin plus titration of glimepiride (mean dose 3.3 mg) with fixed dose metformin plus fixed dose saxagliptin (5 mg daily) in adults 65 years or older.[193] They reported six heart failure events (1.7%) in the metformin plus glimepiride arm compared with three events (0.8%) in the metformin plus saxagliptin arm. The study had about 20 percent loss to followup in each arm. (SOE: Insufficient)

Combination of Metformin Plus a Basal Insulin Versus a Combination of Metformin Plus a Premixed Insulin

In a RCT that compared a combination of insulin glargine daily plus metformin with a combination of insulin lispro 75/25 plus metformin, hospitalization due to heart failure was reported in a single patient on the insulin lispro 75/25 and metformin combination.[223] (SOE: Insufficient)

Strength of Evidence for Congestive Heart Failure

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 90, Table 91, and Table 92 and summarized in the key points. Most studies were RCTs, although five medium-quality observational studies were included. Study limitations for all comparisons were low or medium. In general, we did not find strong differences in outcomes in the lower- versus higher-quality studies. However, many comparisons only had one or two studies, making these quality comparisons difficult. We did not find any evidence of publication bias in any of the comparisons for congestive heart failure. We also did not find any evidence of publication bias or reporting bias in the grey literature review, which would substantially alter our findings (Appendix E). Three studies reported events in one arm only; therefore, we were unable to draw firm conclusions from those studies. While this raises concerns for reporting bias, we expect arms with reporting on this outcome are likely to be the arms where more events occurred. For instance, two of the three studies reported the

congestive heart failure events in the thiazolidinedione arms. However, this inconsistent reporting remains problematic.

Table 90. Strength of evidence domains for monotherapy comparisons in terms of congestive heart failure among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. TZD (shorter studies)	RCTs: 2 (170)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither drug arm favored
Metformin vs. TZD (longer studies)	RCTs: 1(4360)	Medium	Consistent with observational studies	Direct	Imprecise	Undetected	Low	Metformin favored
	Obs: 2 (65,237)	Medium	Consistent with RCT	Direct	Imprecise			
Metformin vs. SU	RCT: 1 (304)	Low	Consistent with observational study	Direct	Imprecise	Undetected	Low	Metformin favored
	Obs: 1 (17,863)	Medium	Consistent with RCT	Direct	Precise			
Metformin vs. DPP-4 inhibitors	RCT: 1 (784)	Medium	Unable to determine	Direct	Imprecise	Undetected	Low	Neither drug favored
TZD vs. SU	RCTs: 4 (11,130)	Low	Consistent	Direct	Imprecise	Undetected	Low	SU favored
	Obs: 2 (116,625)	Medium	Consistent	Direct	Imprecise			
TZD vs. DPP-4 inhibitors	RCT: 1 (655)	Low	Unable to determine	Direct	Imprecise	Undetected	Low	Neither drug favored
SU vs. DPP-4 inhibitors	RCT: 1 (426)	Low	Unable to determine	Direct	Imprecise	Suspected	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; Obs = observational study; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Table 91. Strength of evidence domains for monotherapy versus metformin-based combination comparisons in terms of congestive heart failure among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + TZD	RCT: 3 (2947)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Metformin favored
Metformin vs. metformin + DPP-4 inhibitors	RCT: 4 (3170)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither drug arm favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; RCT = randomized controlled trial; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Table 92. Strength of evidence domains for metformin-based combination comparisons in terms of congestive heart failure among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + TZD vs. metformin + SU	RCT: 1 (305)	Medium	Unable to determine	Direct	Imprecise	Suspected‡	Insufficient	Unable to determine
Metformin + TZD vs. metformin + DPP-4 inhibitors	RCT: 1 (1554)	Medium	Unable to determine	Direct	Imprecise	Suspected‡	Insufficient	Unable to determine
Metformin + SU vs. metformin + DPP-4 inhibitors	RCT: 1 (720)	Low	Unable to determine	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + basal insulin vs. metformin + premixed insulin	RCT: 1 (105)	Medium	Unable to determine	Direct	Imprecise	Suspected‡	Insufficient	Unable to determine

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

‡ Reporting bias was listed as suspected for each of these comparisons, because they did not report events in one of the study arms; however, the arm where the event was not reported is often in the drug arm where one might anticipate that there is likely to be no events.

Evidence for Liver Injury

Monotherapy Comparisons

Metformin Versus Thiazolidinediones

Three RCTs comparing metformin with thiazolidinediones reported on liver injury. Two studies compared metformin with pioglitazone,[62, 70] and one study compared metformin with rosiglitazone.[74] Followup and liver injury definitions varied across studies, and results were mixed. All studies targeted at least 2,000 mg daily in their metformin arms, and doses of thiazolidinediones varied (Table 93). The longer studies were of poorer quality and did not find differences in liver injury between arms. The shortest and largest RCT was a high-quality trial which used the highest doses of the drugs (metformin 2,550 daily maximum dose and pioglitazone 45 mg daily maximum dose) and found more liver injury in the metformin than the pioglitazone arm. (SOE: Low; Neither favored)

Table 93. Randomized controlled trials comparing metformin with thiazolidinediones on liver injury

Author, Year	Study Size (Total N)	Followup	TZD	Definition of Liver Injury	Metformin Events/N (%)	TZD Events/N (%)
Yoon, 2011[74]	349	48 weeks	Rosiglitazone 5.9 mg daily (mean)	Abnormal liver function not defined	0/114 (0)	1/117 (0.85%)
Erem, 2014[70]	60	48 weeks	Pioglitazone started at 15 mg daily (most participants on ≤30 mg daily at end)	Liver enzymes > 2 times ULN	0/13 (0)	0/12 (0)
Schernthaner, 2004[62]	1,199	26 weeks	Pioglitazone started at 30 mg daily; 45 mg daily (maximum)	Liver enzymes > 3 times ULN	2.2%	0.9%

mg = milligrams; TZD = thiazolidinedione; ULN = upper limit normal

Metformin Versus Sulfonylureas

Two RCTs compared metformin with sulfonylureas and reported on liver injury.[50, 74] Neither study provided a specific definition of liver injury, and both studies used sub-maximal doses of the sulfonylurea and comparable doses of metformin (titration to maximum of 2,000 mg daily). ADOPT, the study with long-term followup, found similar rates of liver injury in the two arms,[50] and the other study reported more liver abnormalities in the sulfonylurea arm (Table 94).[74] (SOE: Low; Neither favored)

Table 94. Randomized controlled trials comparing metformin with sulfonylureas on liver injury

Author, Year	Study Size (Total N)	Followup	SU	Definition of Liver Injury	Metformin Events/N (%)	SU Events/N (%)
Kahn, 2006[50] ADOPT Study	4360	Not reported*	Glyburide; started 2.5 mg; maximum 15 mg	Not defined	NR/1341 (1.1)	NR/1441 (0.8)
Yoon, 2011[74]	349	48 weeks	Glimepiride 4.5 mg daily (mean)	Abnormal liver function not defined	0/114 (0)	5/118 (4.24%); *P* = 0.05

ADOPT = A Diabetes Outcome Progression Trial; mg = milligrams; NR = not reported; SU = sulfonylurea
*Study was 6.1 years in duration, but followup for this outcome was not reported.

Thiazolidinediones Versus Sulfonylureas

Three RCTs comparing thiazolidinediones with sulfonylureas reported on liver injury.[50, 52, 74] Followup and liver injury definitions varied (Table 95).

One study reported an non-significant increased risk of liver injury for sulfonylurea versus submaximal rosiglitazone,[74] and the other two RCTs did not find substantial differences in livery injury between arms.[50, 52] Of note, the highest-quality, largest and longest study reported no liver toxicity in either arm.[50] (SOE: Low; Neither favored)

Table 95. Randomized controlled trials comparing thiazolidinediones with sulfonylureas on liver injury

Author, Year	Study Size (Total N)	Followup	TZD	SU	Definition of Liver Injury	TZD Events/N (%)	SU Events/N (%)
Kahn, 2006[50] ADOPT Study	4360	Not reported*	Rosiglitazone 8 mg (maximum)	Glyburide 15 mg daily (maximum)	Not defined	0/1456 (0%)	0/1441 (0%)
Yoon, 2011[74]	349	48 weeks	Rosiglitazone 5.9 mg daily (mean)	Glimepiride 4.5 mg daily (mean)	Abnormal liver function not defined	1/117 (0.85%)	5/118 (4.2%); *P* = 0.05
Tolman, 2009[52]	2120	24 weeks	Pioglitazone 45 mg daily (maximum)	Glyburide 15 mg daily (maximum)	Liver enzymes > 3 times ULN with confirmation	0/1051 (0%)	4/1046 (0.4%) *P* =0.06

ADOPT = A Diabetes Outcome Progression Trial; mg = milligrams; SU = sulfonylurea; TZD = thiazolidinedione; ULN = upper limit of normal
*Study was 6.1 years in duration, but followup time for this outcome was not reported

Sulfonylureas Versus GLP-1 Receptor Agonists

One RCT examined liver injury (defined as hepatobiliary disorders) as an adverse event for this comparison.[110] Seven of 132 participants treated with submaximally-dosed glibenclamide (fixed dose of 1.25 to 2.5 mg daily) developed liver injury at 52 weeks compared with 11 participants of 268 treated with liraglutide titrated to a maximum of 0.9 mg daily (5.3% versus 4.1%).[110] (SOE: Low; Neither favored)

Metformin Versus Metformin-Based Comparisons

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Four RCTs compared metformin with the combination of metformin plus a DPP-4 inhibitor.[146, 152, 160, 164] Followup and liver injury definitions varied (Table 96). In the longest study (52 weeks), both treatments were associated with similar rates of hepatic adverse events (not specified), at a dose of metformin 1000 mg/day.[164] In the shorter studies (12 to 24 weeks), which used higher doses of metformin (1500 mg/day), events were rare, and occurred slightly more often in the metformin plus DPP-4 inhibitor arms.[146, 152, 160] Overall, the lack of clarity on the definition of liver injury precluded conclusions on this outcome for this comparison. (SOE: Insufficient)

Table 96. Randomized controlled trials comparing metformin with metformin plus DPP-4 inhibitors on liver injury

Author, Year	Study Size (Total N)	Followup	DPP-4 Inhibitor	Definition of Liver Injury	Metformin Events/N (%)	Metformin + DPP-4 Inhibitor Events/N (%)
Haak, 2013[164]	567	52 weeks	Linagliptin 5 mg daily	Unspecified hepatic adverse events	13 /170 (7.6%)	11/171 (6.4%)
Wang, 2015[160]	305	24 weeks	Linagliptin 5 mg dialy	Alanine transaminase increase considered to be drug-related	0/100 (0%)	1/205 (0.5%)
Ross, 2012[152]	491	12 weeks	Linagliptin 5 mg daily	Unspecified elevation of liver enzymes	0/44 (0%)	2/224 (0.9%)
Yang, 2011[146]	570	24 weeks	Saxagliptin 5 mg daily	Abnormal liver function	0/142 (0%)	1/146 (0.6%)

DPP-4 = dipeptidyl peptidase-4; mg = milligrams

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

One RCT examined liver injury (defined as hepatic impairment) as an adverse event for the comparison of metformin versus a combination of metformin plus a SGLT-2 inhibitor.[168] None of the 101 participants treated with metformin nor the 199 participants treated with either 5 or 10 mg of canagliflozin developed liver injury at 20 weeks. (SOE: Low; Neither favored)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

Two RCTs compared the combination of metformin plus a thiazolidinedione with the combination of metformin plus a sulfonylurea and reported on liver injury.[179, 185] One trial reported no cases of liver injury (defined as hepatic failure) in the metformin plus pioglitazone arm (0/146; 0%) and one case in the metformin plus glimepiride arm (1/142; 0.7%), at 24 weeks.[185] A smaller 48-week trial reported no cases of liver injury (defined as liver enzymes

values greater than three times the upper limit of normal) in the metformin plus rosiglitazone (0/48) or metformin plus glimepiride (0/47) arms.[179] (SOE: Insufficient)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

A single RCT examined liver injury (defined as alanine aminotransferase or aspartate aminotransferase values greater than three times the upper limit of normal) as an adverse event for the comparison of a combination of metformin plus a sulfonylurea versus a combination of metformin plus a SGLT-2 inhibitor.[201] Three of 482 (0.6%) participants treated with glimepiride (mean daily dose 5.6 mg) developed liver injury (alanine aminotransferase values greater than three times the upper limit of normal) at 104 weeks compared with six of 483 (1.3%) treated with 100 mg canagliflozin and seven of 485 (1.5%) treated with 300 mg canagliflozin. Two participants (0.4%) in the glimepiride arm, five participants (1.1%) in the 100 mg canagliflozin arm, and three participants (0.6%) in the 300 mg canagliflozin arm had aspartate aminotransferase values greater than three times the upper limit of normal. (SOE: Low; Neither favored)

Strength of Evidence for Liver Injury

We found low strength of evidence for the monotherapy comparisons for which there was evidence on liver injury and insufficient evidence for all combination therapy comparisons for this outcome (Table 97). The evidence was limited by a small number of studies with a high risk of bias based on assessment of randomization, masking, and withdrawals. Studies addressing liver injury were generally small and did not use maximal dosing of medications, especially for the non-metformin arms. Also, heterogeneity in definitions of liver injury (or lack of reporting specific definitions) limited the strength of evidence and our ability to make conclusions. A single unpublished study supported findings that neither the combination of metformin plus a sulfonylurea or the combination of metformin plus an SGLT-2 inhibitor were favored for liver injury.

Table 97. Strength of evidence domains for comparisons in terms of liver injury among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. TZD	3 (1608)	High	Inconsistent	Indirect	Imprecise	Undetected	Low	Neither favored
Metformin vs. SU	2 (4709)	High	Inconsistent	Indirect	Imprecise	Undetected	Low	Neither favored
TZD vs. SU	3 (6829)	Medium	Inconsistent	Indirect	Imprecise	Undetected	Low	Neither favored
SU vs. GLP-1 receptor agonists	1 (400)	High	Unknown	Indirect	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + DPP-4 inhibitors	4 (1933)	Low	Unknown	Indirect	Imprecise	Undetected	Insufficient	Unable to determine
Metformin vs. metformin + SGLT-2 inhibitors	1 (299)	Low	Unknown	Indirect	Imprecise	Undetected	Low	Neither favored
Metformin + TZD vs. metformin +SU	2 (723)	High	Inconsistent	Indirect	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + SU vs. metformin + SGLT-2 inhibitors (long-term study)	1 (1450)	Medium	Unknown	Indirect	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Lactic Acidosis

Monotherapy Comparisons

Metformin Versus Sulfonylureas

We identified two short RCTs (lasting 18 and 16 weeks) reporting the rates of lactic acidosis for metformin and sulfonylureas. These RCTs reported no cases of lactic acidosis in any of the treatment arms.[130, 131] (SOE: Low; Neither favored)

Metformin Versus Metformin-Based Comparisons

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

We identified two RCTs (lasting 18 and 16 weeks) reporting the rates of lactic acidosis for metformin and the combination of metformin and a sulfonylurea. These RCTs reported no cases of lactic acidosis in any of the treatment arms.[130, 131] (SOE: Low; Neither favored)

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

One 12-week RCT reported that increased lactic acid blood levels were more frequent in participants treated with metformin alone (3/100; 3%) than in those treated with the combined regimen of metformin with alogliptin (1/96; 1%); the study did not provide a statistical comparison of these rates.[157] Of note, metformin doses were very small in this study (500 to 750 mg daily). (SOE: Insufficient)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a Sulfonylurea

One 24-week RCT compared the rates of lactic acidosis between the combination of metformin and pioglitazone and the combination of metformin and glimepiride. One case of lactic acidosis was reported in the 142 participants (0.7%) receiving metformin plus glimepiride and none were reported in the 146 participants (0%) who received metformin plus pioglitazone.[185] Of note, the participant with lactic acidosis was noted to have had multiple serious adverse events including heart failure, liver failure, renal failure, and electrolyte disturbances. (SOE: Low; Combination of metformin plus a thiazolidinedione favored)

Strength of Evidence for Lactic Acidosis

Few studies addressed lactic acidosis, and evidence was of low strength or insufficient when present (Table 98). The evidence was at low or medium risk of bias, and studies were small and brief in duration; thus the evidence was imprecise and consistency unknown. One of the four studies addressing lactic acidosis only reported on elevated blood levels of lactic acidosis and not on the clinical syndrome of lactic acidosis.

Table 98. Strength of evidence domains for comparisons in terms of lactic acidosis among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. SU	2 (886)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + SU	2 (886)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + DPP-4 inhibitors	1 (288)	Low	Unknown	Indirect	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + TZD vs. metformin +SU	1 (288)	High	Unknown	Direct	Imprecise	Undetected	Low	Metformin + TZD favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Pancreatitis

Monotherapy Comparisons

Metformin Versus DPP-4 Inhibitors

A 26-week trial compared metformin (1,000 mg daily; n=109), metformin (2,000 mg daily; n=111), and alogliptin (25 mg daily; n=112) and actively ascertained for pancreatitis and found no cases of pancreatitis in these arms.[84] (SOE: Low; Neither favored)

Metformin Versus GLP-1 Receptor Agonists

A 52-week RCT that compared metformin with dulaglutide reported no cases of pancreatitis (defined as a lipase increase higher than three times the upper limit) in any of the 268 participants receiving metformin or the 269 participants receiving dulaglutide.[91] (SOE: Low; Neither favored)

Thiazolidinediones Versus GLP-1 Receptor Agonists

A single RCT compared pioglitazone (maximum tolerated dose up to 45 mg/day) with exenatide titrated to 10 µg twice daily and reported no cases (0/136, 0%) of pancreatitis in the pioglitazone arm and a single case (1/142, 0.7%) in the exenatide arm at 48 weeks.[105] Pancreatitis was not defined, and the method of ascertainment was not reported.[105] (SOE: Low; Pioglitazone favored)

Sulfonylureas Versus DPP-4 Inhibitors

We identified one RCT comparing the incidence of pancreatitis between sulfonylurea and DPP-4 inhibitors at 52 weeks.[106] There were no cases of pancreatitis in any of the 76 participants receiving glimepiride or the 151 participants receiving linagliptin. The definition of pancreatitis was unspecified. (SOE: Low; Neither favored)

Sulfonylureas Versus GLP-1 Receptor Agonists

Two RCTs compared sulfonylureas with GLP-1 receptor agonists and reported on pancreatitis.[109, 112] One trial reported two cases of pancreatitis in the liraglutide arm (2/498; 0.4%) and no cases in the glimepiride arm (0/248; 0%) at 104 weeks.[112] A 24-week trial reported no cases of pancreatitis in the liraglutide (n=272) or glibenclamide (n=139) arms.[109] The criteria for a diagnosis of pancreatitis was unspecified in both studies. (SOE: Low; Sulfonylureas favored)

DPP-4 Inhibitors Versus GLP-1 Receptor Agonists

A 26-week RCT that compared liraglutide (n = 446) with sitagliptin (n = 219) reported no episodes of pancreatitis.[210] The definition of pancreatitis was unspecified. (SOE: Low; Neither favored)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

A single RCT with long-term followup compared the incidence of pancreatitis with metformin to the combination of metformin plus a sulfonylurea.[141] There were no cases of pancreatitis, at 104 weeks of followup, among the 100 participants who received monotherapy or the 302 participants who received combined therapy. Criteria for pancreatitis was enzymatic elevation at three times the upper limit plus clinical symptoms. (SOE: Low; Neither favored)

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

We identified 11 RCTs comparing the incidence of pancreatitis with metformin with the combination of metformin plus a DDP-4 inhibitor.[51, 84, 141, 151, 152, 157, 159, 160, 162, 164, 256] Definitions of pancreatitis and duration of followup differed across studies (Table 99). Four RCTs did not describe active ascertainment of pancreatitis,[51, 160, 164, 256] and three RCTs had substantial losses to followup.[51, 84, 141] Pancreatitis was rare, with events in only three of the 11 studies. In the study of longer duration, rates of pancreatitis were similar (0.6%) across arms at 52 weeks.[159] Events were reported in only the metformin plus DPP-4 inhibitor arms in the two shorter studies.[84, 162] (SOE: Low; Neither favored)

Table 99. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on pancreatitis

Author, Year	Study Size	Followup	DPP-4 Inhibitor	Definition of Pancreatitis	Metformin Events/N	DPP-4 Inhibitor Events/N
Bergenstal, 2012[51]	666	156 weeks	Sitagliptin 100 mg daily	Unspecified	0/93	0/184
Ahren, 2014[141]	1049	104 weeks	Sitagliptin 100 mg daily	Enzymes elevation > 3ULN + clinical symptoms Adjudicated	0/100	0/299
Nauck, 2014[159]	1098	52 weeks	Sitagliptin 100 mg daily	Enzymes elevation > 3ULN + clinical symptoms Adjudicated	1/177 (0.6%)	2/315 (0.6%)
Skrivanek, 2014[256]	230	26 weeks	Sitagliptin 100 mg daily	Unspecified elevation of enzymes	0/38	0/42
Pratley, 2014[84]	784	26 weeks	Alogliptin 25 mg daily	Unspecified elevation of enzymes	0/222	2/220 (0.9%) 1 case confirmed
Seino, 2012[157]	288	12 weeks	Alogliptin 12.5 or 25 mg daily	Unspecified	0/100	12.5 mg: 0/92 25 mg: 0/96
Haak, 2013[164]	567	52 weeks	Linagliptin 5 mg	Clinical diagnosis	0/170	0/396
Wang, 2015[160]	305	24 weeks	Linagliptin 5 mg	Unspecified	0/100	0/205
Ji, 2015[162]	689	14 weeks	Linagliptin 5 mg	Unspecified	0/345	1/344 (0.3%)
Ross, 2012[152]	491	12 weeks	Linagliptin 5 mg	Unspecified	0/44	0/447
White, 2014[151]	160	12 weeks	Saxagliptin 5 mg	Unspecified	0/78	0/66

DPP-4 = dipeptidyl peptidase-4; mg = milligrams; ULN = upper limit of normal

Metformin Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

Three RCTs compared the incidence of pancreatitis with metformin and the combination of metformin plus a GLP-1 receptor agonist (Table 100).[141, 159, 256] The longest study actively ascertained for pancreatitis but had substantial losses to followup. In this study with 104 weeks of followup, two cases of pancreatitis were reported in the metformin plus GLP-1 receptor agonist arm (2/296, 0.7%) and none were reported in the metformin arm (0/100, 0%).[141] Results from the other two RCTs, which were brief in duration, were mixed. One reported no pancreatitis in either arm at 26 weeks but did not report on active ascertainment,[256] and the other reported a single case of pancreatitis in the metformin monotherapy arm and no cases of pancreatitis in the combination arm and did actively ascertain for pancreatitis.[159] (SOE: Low; Metformin favored)

Table 100. Randomized controlled trials comparing metformin with a combination of metformin plus a GLP-1 receptor agonist on pancreatitis

Author, Year	Study Size (Total N)	Followup	GLP-1 Receptor Agonist	Definition of Pancreatitis	Metformin Events/N (%)	DPP-4 inhibitor Events/N
Skrivanek, 2014[256]	230	26 weeks	Dulaglutide 0.75, 1.0, and 1.5 mg weekly	Unspecified elevation of enzymes	0/38	0.75 mg: 0/21 1.0 mg: 0/10 1.5 mg: 0/25
Nauck, 2014[159]	1098	52 weeks	Dulaglutide 0.75 and 1.5 mg weekly	Enzymes elevation > 3ULN + clinical symptoms Adjudicated	1/177 (0. 5%)	0.75 mg: 0/302 1.5 mg: 0/304
Ahren, 2014[141]	1049	104 weeks	Albiglutide 50 mg weekly (maximum)	Enzymes elevation > 3ULN + clinical symptoms Adjudicated	0/100	2/296 (0.7%)

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; mg = milligrams; ULN = upper limit of normal

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a DPP-4 Inhibitor

The 26-week DURATION-2 RCT reported two cases of pancreatitis in the 165 participants who were treated with the metformin plus pioglitazone (2/165, 1.2%) combination compared with none of the 166 participants who received the metformin plus sitagliptin combination (0/166, 0%).[188] Pancreatitis was not actively ascertained, and criteria for diagnosis were unspecified; this study had differential losses to followup across the arms (metformin plus thiazolidinedione, 21%; metformin plus DPP-4 inhibitor, 13%). (SOE: Low; Combination of metformin plus a DPP-4 inhibitor favored for short-term risk of pancreatitis)

Combination of Metformin Plus a Thiazolidinedione Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

The DURATION-2 RCT described above had an additional arm with 160 participants who received metformin plus weekly exenatide, and none were reported to have pancreatitis during the study.[188] Again, two of 165 participants had pancreatitis in the metformin plus

thiazolidinedione arm; pancreatitis was not actively ascertained, and criteria for diagnosis were unspecified. This study had large losses to followup across the arms (21% in both the metformin plus thiazolidinedione and metformin plus exenatide arms).[188] (SOE: Low; Combination of metformin and GLP-1 receptor agonist favored for short-term risk of pancreatitis)

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

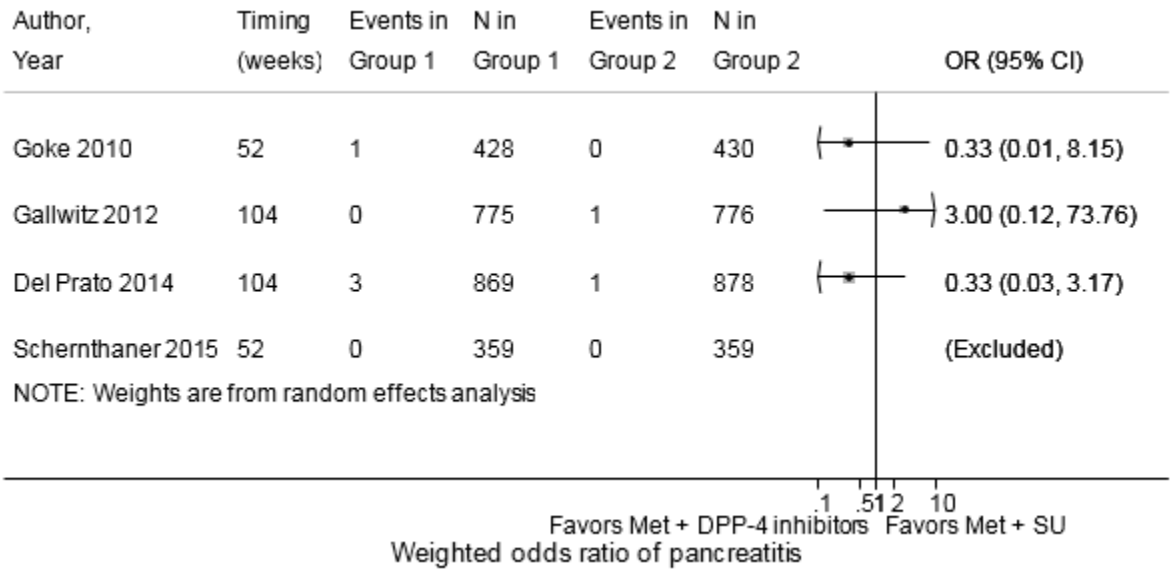
We identified four RCTs which compared the incidence of pancreatitis for the combination of metformin plus a sulfonylurea with the combination of metformin plus a DPP-4 inhibitor.[193-195, 197] Event rates were low in both arms across studies. Results were inconsistent across the studies of longer duration (104 weeks) and across the shorter studies (52 weeks) (Table 101, Figure 88). Only one study reported active ascertainment of pancreatitis,[197] and losses to followup were substantial in all four studies.[193-195, 197] (SOE: Insufficient for long-term and short-term risk)

Table 101. Randomized controlled trials comparing the combination of metformin plus a sulfonylurea with the combination of metformin plus a DPP-4 inhibitor for pancreatitis

Author, Year	Study Size (Total N)	Followup	SU	DPP-4 Inhibitor	Definition of Pancreatitis	SU Events/N (%)	DPP-4 Inhibitor Events/N
Del Prato, 2014[197]	2620	104 weeks	Glipizide 5 mg mean daily dose	Alogliptin 12.5 or 25 mg arms	Confirmed by laboratory and imaging tests (not defined)	3/869 (0.3%)	Alogliptin 12.5 mg: 0/873 (0%) Alogliptin 25 mg: 1/878 (0.1%)
Goke, 2010[195]	858	52 weeks	Glipizide 14.7 mg mean daily dose	Saxagliptin 5 mg daily	Not defined	1/428 (0.2%)	0/430 (0%)
Gallwitz, 2012[194]	1552	104 weeks	Glimepiride 3 mg mean daily dose	Linagliptin 5 mg daily	Not defined	0/775 (0%)	1/776 (0.1%)
Schernthaner, 2015[193]	718	52 weeks	Glimepiride 3.3 mg mean daily dose	Saxagliptin 5 mg daily	Not defined	0/359 (0%)	0/359 (0%)

DPP-4 = dipeptidyl peptidase-4; mg = milligrams; SU = sulfonylurea

Figure 88. Odds ratio of pancreatitis comparing the combination of metformin plus a sulfonylurea with the combination of metformin plus a DPP-4 inhibitor



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; Group 1 = metformin plus a sulfonylurea; Group 2 = metformin plus a DPP-4 inhibitor; Met = metformin; OR = odds ratio; SU = sulfonylurea
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

We identified two relevant RCTs.[53, 204] A 104-week RCT comparing metformin plus glimepiride (N=508) versus metformin plus exenatide (N = 511) reported one case of pancreatitis in each arm (0.2% in each arm).[53] A 16-week RCT comparing metformin plus glimepiride (N=231) versus metformin plus liraglutide (N = 467) reported no cases of pancreatitis in either arm.[204] Studies did not report active ascertainment of pancreatitis, and the criteria for pancreatitis diagnosis were unspecified. (SOE: Low; Neither favored)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

A single RCT (N=355), with 24 weeks of followup, reported no cases of pancreatitis for metformin plus saxagliptin or metformin plus dapagliflozin.[209] Pancreatitis was not defined, and the method of ascertainment was not described.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Receptor Agonist

The 26-week DURATION-2 RCT reported no cases of pancreatitis in either the metformin plus weekly exenatide (n=160) or metformin plus sitagliptin arm (n=166). Pancreatitis was not actively ascertained, and criteria for diagnosis of pancreatitis were unspecified. This study had differential losses to followup across the arms (metformin plus GLP-1 receptor agonist, 21%; metformin plus DPP-4 inhibitor, 13%).[188] (SOE: Low; Neither favored for short-term pancreatitis risk)

Strength of Evidence for Pancreatitis

The published evidence on the comparative safety of the medications of interest was of low-strength or insufficient (Table 102, Table 103, and Table 104). The evidence was mainly limited by a lack of studies and further limited by the short duration of studies and low (expected) event rates. All evidence came from RCTs but tended to be at medium to high risk of bias, mainly because of the availability of only a few fair- to poor-quality studies for each comparison. Consistency tended to be indeterminate because of a lack of more than one study for many comparisons. All evidence was direct, although active ascertainment and definitions were not usually provided in studies. The small number of studies and their small sample sizes contributed to the evidence being imprecise for all comparisons for which we had studies. We identified unpublished studies which could have affected our grading of the evidence, but the evidence would likely only have been strengthened to a rating of low. One unpublished study confirmed the findings of the single published study that thiazolidinediones are favored over GLP-1 receptor agonists for pancreatitis. Two unpublished studies with long-term followup would have likely supported a conclusion of metformin plus a DPP-4 inhibitor being favored over metformin plus a sulfonylurea regarding long-term pancreatitis risk with low strength of evidence. One of these unpublished studies with long-term followup suggested increased risk of pancreatitis (long-term) for metformin plus a GLP-1 receptor agonist compared with metformin plus a DPP-4 inhibitor; this was in contrast to the single published study that suggested no difference in short-term risk of pancreatitis.

We identified an unpublished study comparing thiazolidinediones to DPP-4 inhibitors, a comparison for which we had no published evidence.

Table 102. Strength of evidence domains for monotherapy comparisons in terms of pancreatitis among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. DPP-4 inhibitors	1 (784)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. GLP-1 receptor agonists	1 (495)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
TZD vs. GLP-1 receptor agonists	1 (278)	High	Unknown	Direct	Imprecise	Suspected	Low	TZD favored
SU vs. DPP-4 inhibitors	1 (227)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
SU vs. GLP-1 receptor agonists	2 (1210)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	SU favored
DPP-4 inhibitors vs. GLP-1 receptor agonists	1 (661)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating the outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Table 103. Strength of evidence domains for metformin monotherapy versus metformin-based combination comparisons in terms of pancreatitis among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + SU (long-term study)	1 (1049)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin vs. metformin + DPP-4 inhibitors (long-term and short-term studies)	11 (6327)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored for long-term or short-term pancreatitis risk
Metformin vs. metformin + GLP-1 receptor agonists	3 (2377)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Metformin favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating the outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Table 104. Strength of evidence domains for metformin-based combination comparisons in terms of pancreatitis among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin + TZD vs. metformin + DPP-4 inhibitors	1 (491)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin + DPP-4 inhibitor favored for short-term risk of pancreatitis
Metformin + TZD vs. metformin + GLP-1 receptor agonists	1 (491)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Metformin + GLP-1 receptor agonist favored for short-term risk of pancreatitis
Metformin + SU vs. metformin + DPP-4 inhibitors (longer duration studies)	2 (4172)	High	Inconsistent	Direct	Imprecise	Suspected	Insufficient	Unable to determine for long-term risk of pancreatitis
Metformin + SU vs. metformin + DPP-4 inhibitors (shorter duration study)	2 (1576)	High	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + SU vs. metformin + GLP-1 receptor agonists	2 (2481)	High	Consistent	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors (shorter duration study)	1 (355)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored
Metformin + DPP-4 inhibitors vs. metformin + GLP-1 receptor agonists (short duration study)	1 (491)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither treatment favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating the outcome.

† Unless otherwise specified, the estimates are the pooled odds ratio (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Severe Allergic Reactions

Monotherapy Comparisons

Metformin Versus GLP-1 Receptor Agonists

A single 52-week RCT (N=495) that compared metformin with dulaglutide reported no systemic hypersensitivity reaction in either arm.[91] (SOE: Low; Neither favored)

Thiazolidinediones Versus GLP-1 Receptor Agonists

A single RCT (N=278) that compared pioglitazone with exenatide reported no systemic hypersensitivity reaction in either arm at 48 weeks of followup.[105] (SOE: Low; Neither favored)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Four RCTs compared the incidence of severe allergic reactions between metformin and the combination of metformin plus a DDP-4 inhibitor (Table 105).[146, 151, 152, 164] Heterogeneity in definitions of severe allergic reactions and duration of followup precluded a meta-analysis. Three of the four RCTs reported slightly higher rates of hypersensitivity reaction events in the metformin plus DPP-4 inhibitor versus the metformin monotherapy arms.

The longest RCT was a 54-week extension study[164] in which the arms included participants from the initial 6-month study[86] and participants who were re-randomized for the extension study. Among participants who were newly randomized for the 54-week extension study, hypersensitivity reactions occurred in 0 percent of the metformin 2000 mg arm, 0 percent of the metformin 1000 mg plus linagliptin 5 mg arm, and in 1.7 percent of the metformin 2000 mg plus linagliptin 5 mg arm. (SOE: Low; Metformin favored)

Table 105. Randomized controlled trials comparing metformin with a combination of metformin plus a DPP-4 inhibitor on severe allergic reactions

Author, Year	Sample Size (Total N)	Followup	DPP-4 Inhibitor	Definition of Severe Allergic Reaction	Active Asc.	Metformin Events/N (%)	DPP-4 Inhibitor Events/N (%)
Haak, 2013[164]	567	54 weeks	Linagliptin 5 mg	Hypersensitivity reactions (e.g., angioedema, anaphylaxis) Severe cutaneous reactions	Yes Yes	1/170 (0.6%)* 0/170	2/171 (1.2%)* 0/171
White, 2014[151]	160	12 weeks	Saxagliptin 5 mg	Hypersensitivity reactions	NR	0/78	0/66
Yang, 2011[146]	570	24 weeks	Saxagliptin 5 mg	Hypersensitivity reactions	Yes	0/287	3/283 (1.1%)
Ross, 2012[152]	491	12 weeks	Linagliptin	Hypersensitivity reactions (angioedema, anaphylaxis, angioedema-like)	Yes	0/44	5 mg: 1/224 (0.4%) 2.5 mg: 0/223

Asc = ascertainment; DPP-4 = dipeptidyl peptidase-4; mg = milligrams

* Data are shown for the metformin 2000 mg monotherapy arm and the metformin 2000 mg plus linagliptin 5 mg combination arm; there were no events reported in the metformin 1000 mg plus linagliptin combination arm.

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

A single 52-week RCT compared metformin plus glipizide with metformin plus saxagliptin and reported on hypersensitivity adverse events.[195] The authors reported a hypersensitivity adverse event in one participant in the metformin plus saxagliptin arm and in two participants in the metformin plus glipizide arm. One of the events in the metformin plus glipizide arm was noted to be related to ciprofloxacin. This study did not provide information on the method of ascertainment or definition of hypersensitivity. This RCT also had high rates of discontinuation based partly on increasingly strict glycemic control criteria for maintaining eligibility in the study.[195] (SOE: Low; Neither favored)

Strength of Evidence for Severe Allergic Reactions

We identified evidence for three comparisons for the outcome of allergic reactions (Table 106). The published studies were on comparisons that included GLP-1 receptor agonists and DPP-4 inhibitors. All evidence was low or insufficient for this outcome. Because of the limited numbers of studies and their samples sizes, evidence was imprecise. We did not detect reporting bias, but our assessment of this was also limited by the small number of studies.

Table 106. Strength of evidence domains for comparisons in terms of severe allergic reactions among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. GLP-1 receptor agonists	1 (495)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
TZD vs. GLP-1 receptor agonists	1 (278)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + DPP-4 inhibitors	4 (1788)	Low	Consistent	Direct	Imprecise	Undetected	Low	Metformin favored
Metformin + SU vs. metformin + DPP-4 inhibitors	1 (858)	High	Unknown	Direct	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating the outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Macular Edema or Decreased Vision

Monotherapy Comparisons

Thiazolidinediones Versus GLP-1 Receptor Agonists

A single RCT examined blurred vision.[105] Three of 136 participants (2.2%) treated with pioglitazone and two of 142 participants (1.4%) treated with exenatide had blurred vision over 48 weeks of followup. (SOE: Low; Neither favored)

Sulfonylureas Versus GLP-1 Receptor Agonists

One 104-week RCT compared glimepiride with liraglutide at two different doses (1.2 and 1.8 mg) and reported on decreased vision.[113] At the end of the study, the incidence of decreased vision was comparable in all arms, with 7 percent of the glimepiride participants (n=248) having decreased vision compared with 6 percent of the liraglutide participants (n=251 for liraglutide at 1.2 mg and n=247 for liraglutide at 1.8 mg). (SOE: Low; Neither favored)

Strength of Evidence for Macular Edema or Decreased Vision

We identified only two studies for the outcomes of macular edema or decreased vision which evaluated different comparisons. Therefore, the evidence on these outcomes was insufficient because of a lack of studies (Table 107).

Table 107. Strength of evidence domains for monotherapy comparisons in terms of macular edema or decreased vision among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
TZD vs. GLP-1 receptor agonists	1 (278)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
SU vs. GLP-1 receptor agonists (long-term study)	1 (746)	Medium	Unknown	Direct	Imprecise	Undetected	Low	Neither favored

GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the safety outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Urinary Tract Infections

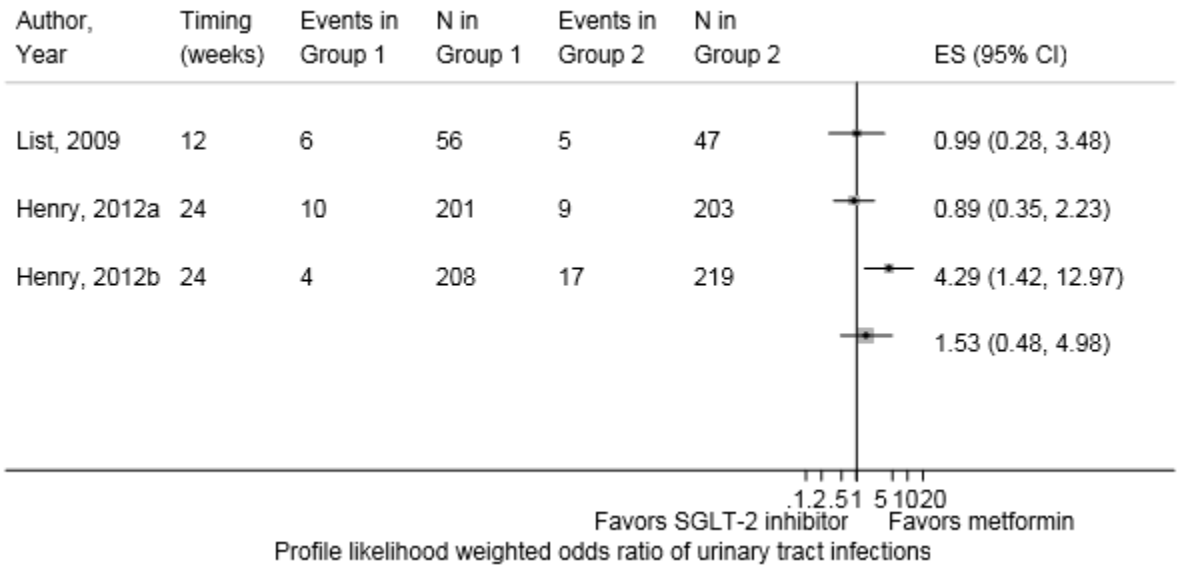
Monotherapy Comparisons

Metformin Versus SGLT-2 Inhibitors

Three short RCTs (published in two articles), 12 to 24 weeks in duration, compared dapagliflozin with metformin and reported on UTIs.[88, 89] Since ORs did not appear to vary by gender in these short-term studies, we present results for men and women combined. We found significant statistical heterogeneity using a random effects meta-analysis (pooled OR, 1.54; 95% CI, 0.56 to 4.22; I-squared, 61.1%). Exclusion of any one study did not change the inference of the meta-analysis. We found similar non-significant increased odds for SGLT-2 inhibitors versus metformin for UTIs (pooled OR, 1.5; 95% CI, 0.5 to 5.0 (Figure 89) using the profile likelihood method. One of the RCTs used a lower dose of dapagliflozin of 5 mg[88] relative to 10 mg in the other two RCTs.

We did not include one RCT in the meta-analysis because it was longer (78 weeks) than the other three studies.[90] This study compared metformin to 10 mg of empagliflozin and 25 mg of empagliflozin and reported similar overall incidences of UTIs with both doses of empagliflozin. UTI rates among men receiving 25 mg of empagliflozin (4/57; 7.0%) were non-significantly higher than among those receiving 10 mg of empagliflozin (0/49; 0%) and metformin (0/28; 0%) and approached UTI rates among women [empagliflozin 10 mg: 4/57 (7.0%), empagliflozin 25 mg: 3/52 (5.8%), and metformin: 2/28 (7.1%)].[90] (SOE: Low; Neither favored)

Figure 89. Pooled odds ratio of urinary tract infections comparing metformin with SGLT-2 inhibitors



CI = confidence interval; Group 1 = metformin; Group 2 = sodium-glucose co-transporter-2 inhibitors; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

One 24-week RCT compared 100 mg of sitagliptin with 10 mg and 25 mg of empagliflozin and reported UTI events separately by gender.[114] UTI occurrences among men were similar in those receiving sitagliptin (4/141; 3%) versus 10 mg of empagliflozin (3/142; 2%) and 25 mg of empagliflozin (2/144; 1%).[114] UTI events were non-significantly lower in women receiving sitagliptin (7/82; 9%) versus 10 mg of empagliflozin (12/82; 15%) and 25 mg of empagliflozin (10/78; 13%). The study did not test for an interaction by gender. (SOE: Low; Neither favored in men, DPP-4 inhibitors favored in women)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Nine short-term RCTs (published in six articles) compared metformin with the combination of metformin plus an SGLT-2 inhibitor and showed similar rates of UTIs for the combination compared to metformin (pooled OR, 1.2; 95% CI, 0.7 to 1.9) (Figure 90).[88, 153, 156, 165, 166, 168] No single study markedly influenced the results, and we did not find evidence of substantial statistical heterogeneity ($I^2 = 0.0\%$). One study also reported that no events of urosepsis or pyelonephritis occurred in either arm.[166] The definitions for UTIs varied across studies (Table 108).

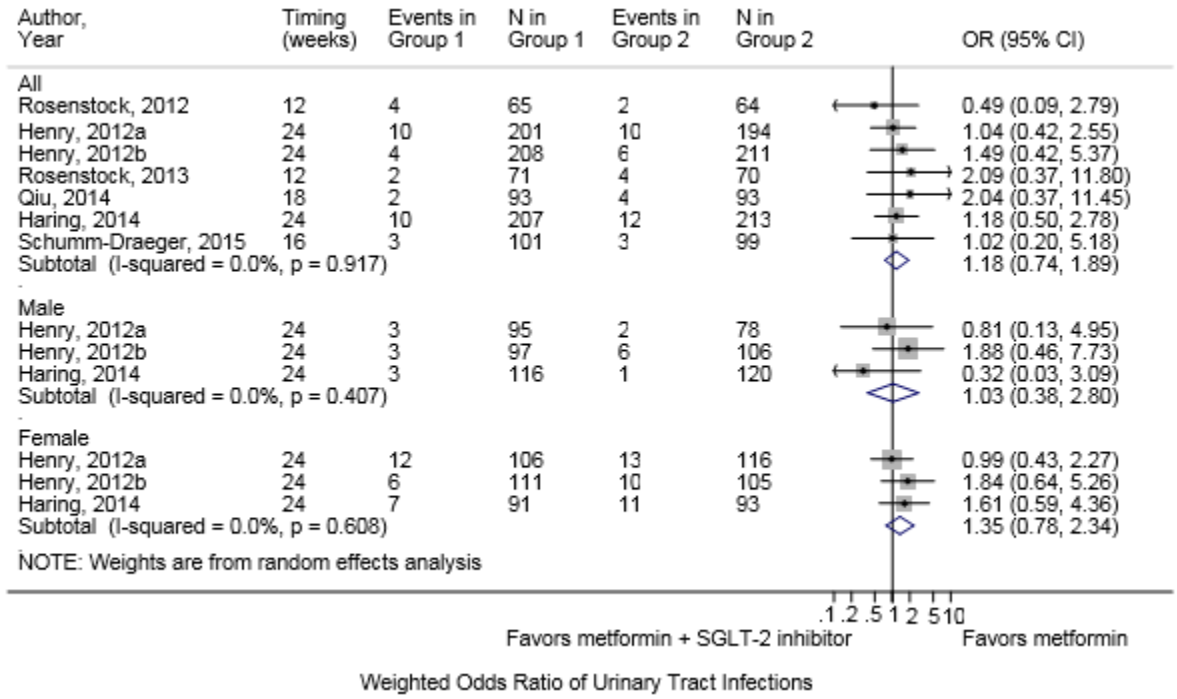
Table 108. Definitions of urinary tract infections used in randomized controlled trials comparing metformin with a combination of metformin and SGLT-2 inhibitor

Author, Year	Definition of UTI Outcome (Actively Ascertained Unless Otherwise Noted)
Bailey, 2013[170]	UTI (does not include events suggestive of UTI)
Rosenstock, 2012[156]	UTI, not otherwise specified
Henry, 2012[88]	Events suggestive of UTI
Bolinder, 2014[267]	MedDRA definition of UTI
Rosenstock, 2013[153]	UTI, not otherwise specified
Qiu, 2014[165]	UTI, not otherwise specified
Haring, 2014 (a)[166]	MedDRA definition for UTI
Henry, 2012 (b)[88]	Based on a predefined list of signs, symptoms and other events suggestive of UTI
Schumm-Draeger, 2015[168]	MedDRA definition of UTI

MedDRA = Medical Dictionary for Regulatory Activities; UTI = urinary tract infection

Based on three studies providing gender-stratified results, meta-analyses stratified by gender showed that women had non-significantly increased odds of UTIs for the combination of metformin plus an SGLT-2 inhibitor versus metformin (pooled OR, 1.4; 95% CI, 0.8 to 2.3) and no difference in UTI odds between treatment groups for men (pooled OR, 1.0; 95% CI, 0.4 to 2.8).[88, 166]

Figure 90. Pooled odds ratio of short-term risk of urinary tract infections comparing metformin with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

We did not include two moderately-sized RCTs (total sample size, 182 to 546) in the meta-analysis because they were longer (102 weeks).[170, 267] One compared metformin with metformin plus dapagliflozin and reported UTI rates of 5.8 percent and 11.9 percent in the metformin and metformin plus dapagliflozin arms, respectively.[170] The other had similar UTI rates across arms (metformin, 4.4% and dapagliflozin, 3.3%).[267] Of note, the former had very high losses to followup with 47 percent losses in the metformin arm compared with 30 percent to 40 percent in the other arms.[170] (SOE: Low; Neither favored)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Three RCTs compared metformin plus a sulfonylurea with metformin plus an SGLT-2 inhibitor and reported inconsistent results regarding UTIs (Table 109).[54, 200, 201] We did not combine these studies in a meta-analysis because of the heterogeneity in the definition of UTI and study durations. Two 104-week RCTs compared metformin plus glimepiride to metformin plus an SGLT-2 inhibitor and found similar incidences of UTIs across arms.[200, 201] A 208-week RCT reported more UTIs in the metformin plus dapagliflozin arm compared to the metformin plus glipizide arm.[54] This study reported high withdrawal rates of greater than 60 percent in each

arm.[54] UTI rates were lower among men compared to women when reported by gender.[54, 200] (SOE: Low; Neither favored)

Table 109. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor on urinary tract infections

Author, Year	Definition of UTI Outcome*	Results Events/N (%)
Leiter, 2015[201]	Cystitis, pyelonephritis chronic, and UTI[198]	Metformin + glimepiride: 33/482 (7%) Metformin + canagliflozin 100 mg: 51/483 (11%) Metformin + canagliflozin 300 mg: 42/485 (9%)
Del Prato, 2015[54]	Confirmed UTI, not otherwise defined	Female Metformin + glipizide: 25/408 (13.5%) Metformin + dapagliflozin: 35/406 (19.4%) Male Metformin + glipizide: 13/408 (5.8%) Metformin + dapagliflozin: 20/406 (8.8%)
Ridderstrale, 2014[200]	MedDRA definition of UTI (passive ascertainment)	Female Metformin + glimepiride: 81/359 (23%) Metformin + empagliflozin: 74/333 (22%) Male Metformin + glimepiride: 21/421 (5%) Metformin + empagliflozin: 31/432 (7%)

MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams; UTI = urinary tract infections
* Outcomes are actively ascertained unless otherwise noted.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Five RCTs compared metformin plus DPP-4 with metformin plus an SGLT-2 inhibitor and reported inconsistent results (Table 110). We did not combine these studies because of differences in study duration and dosing.[90, 153, 156, 158, 209]

The longest RCT (78 weeks) was of low quality and reported UTI rates stratified by sex. Among women, UTI rates were higher for the metformin plus empagliflozin 25 mg arm relative to the other arms; among men, UTI rates were highest in the metformin plus sitagliptin arm relative to the other arms.[90] A medium-quality, 52-week RCT compared metformin plus sitagliptin to metformin plus canagliflozin at doses of 100 mg and 300 mg and reported slightly lower UTI rates in the highest-dose (300 mg) canagliflozin arm and slightly higher rates in the lower-dose (100 mg) canagliflozin arm.[158]

Three short-term studies also conflicted. One medium-quality study reported a higher UTI rate with metformin plus 200 mg of canagliflozin compared with the other arms.[156] Two high-quality short-term RCTs found similar UTI rates in the metformin plus DPP-4 inhibitor arms and metformin plus SGLT-2 inhibitor arms.[153, 209] The evidence was graded as being at medium risk of bias because of failure to report clearly on the randomization scheme. (SOE: Low; Neither favored)

Table 110. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus an SGLT-2 inhibitor on urinary tract infections

Author, Year	Followup	Definition of UTI Outcome*	Results Events/N (%)
Rosenstock, 2012[156]	12 weeks	UTI, not otherwise specified	Metformin + sitagliptin 100 mg: 1/65 (2%) Metformin + canagliflozin 100 mg: 2/64 (3%) Metformin + canagliflozin 200 mg: 6/65 (9%) Metformin + canagliflozin 300 mg: 2/64 (3%)
Rosenstock, 2013[153]	12 weeks	UTIs, including cystitis, excluding signs and symptoms	Metformin + sitagliptin 100 mg: 4.2% Metformin + empagliflozin 10 mg: 4.2% Metformin + empagliflozin 25 mg: 5.7%
Rosenstock, 2015[209]	24 weeks	UTI, not otherwise specified	Metformin + saxagliptin 5 mg: 9/176 (5%) Metformin + dapagliflozin 10 mg: 7/179 (5%)
Lavalle-Gonzalez, 2013[158]	52 weeks	UTI, not otherwise specified	Metformin + sitagliptin 100 mg: 23/366 (6.3%) Metformin + canagliflozin 100 mg: 29/368 (7.9%) Metformin + canagliflozin 300 mg: 18/367 (4.9%)
Ferrannini, 2013[90]	78 weeks	MedDRA definition of UTI	Female Metformin + sitagliptin 100 mg: 4/27 (14.8%) Metformin + empagliflozin 10 mg: 13/83 (15.7%) Metformin + empagliflozin 25 mg: 18/78 (23.1%) Male Metformin + sitagliptin 100 mg: 3/29 (10.3%) Metformin + empagliflozin 10 mg: 2/83 (2.4%) Metformin + empagliflozin 25 mg: 3/88 (3.4%)

MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams; UTI = urinary tract infections
* Outcomes are actively ascertained unless otherwise noted.

Strength of Evidence for Urinary Tract Infections

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 111 and summarized in the key points. All studies were RCTs. Study limitations for all the comparisons were low or medium. Although evidence of gender differences in UTI rates was limited, the data suggest that there may be higher rates of UTIs among females (particularly noted in the comparisons of metformin versus metformin plus SGLT-2 inhibitor). In general, we did not find strong differences in outcomes in the lower- versus higher-quality studies. We did not find any evidence of publication bias in any of the comparisons for UTI. The grey literature was consistent with our findings in the metformin plus SU vs. metformin plus SGLT-2 inhibitor comparison, with one unpublished study that found no UTIs in either arm.

Table 111. Strength of evidence domains for monotherapy and metformin-based combination comparisons in terms of urinary tract infections among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. SGLT-2 inhibitors	4 (2,292)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored for short-term UTI risk
DPP-4 inhibitors vs. SGLT-2 inhibitors	1 (899)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored in men DPP-4 inhibitors favored in women
Metformin vs. metformin + SGLT-2 inhibitors	9 (4,035)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored for short-term UTI risk
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer studies)	3 (3,815)	Low	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored for long-term risk of UTI
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	5 (3,423)	Medium	Inconsistent	Direct	Precise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Impaired Renal Function

Monotherapy Comparisons

Metformin Versus SGLT-2 Inhibitors

Three RCTs compared metformin with SGLT-2 inhibitors and reported on impaired renal function (Table 112).[89, 90, 239] We did not combine the results of these RCTs in a meta-analysis because they varied greatly in their definitions of impaired renal function.

Two trials evaluated the change in estimated glomerular filtration rate (eGFR) and found no substantial differences between the arms.[89, 90]

One 12-week trial (N=408) evaluated incident microalbuminuria, change in the urine albumin-to-creatinine ratio, and incident diabetic nephropathy.[239] The investigators did not find substantial differences in urine albumin-to-creatinine ratio across arms, and those in the low-dose empagliflozin arm had more incident microalbuminuria and diabetic nephropathy compared with the metformin and high-dose empagliflozin arm. (SOE: Low; Neither favored)

Table 112. Randomized controlled trials comparing metformin with SGLT-2 inhibitors on impaired renal function

Author, Year	Followup	Definition of Impaired Renal Function*	Results
List, 2009[89]	12 weeks	eGFR	NR for any arm Qualitative statement of no difference across groups
Ferrannini, 2013[90]	90 weeks	eGFR (ml/min/1.73 m^2)	Metformin vs. empagliflozin 10 mg: between-group difference from baseline to final, 0.13 (95% CI, -4.5 to 4.7) Metformin vs. empagliflozin 25 mg: between-group difference from baseline to final, 2.66 (95% CI, -1.8 to 7.1)
Ferrannini, 2013[239]	12 weeks	Microalbuminuria, not further defined	Metformin: 1.3% Empagliflozin 10 mg: 3.7% Empagliflozin 25 mg: 0%
	12 weeks	Diabetic nephropathy (unclear if actively ascertained)	Metformin: 1.3% Empagliflozin 10 mg: 2.5% Empagliflozin 25 mg: 1.2%
	12 weeks	Urinary albumin to creatinine ratio (mg/mmol)	Metformin vs. empagliflozin 10 mg: between-group difference from baseline to final, 0.08 mg/mmol Metformin vs. empagliflozin 25 mg: between-group difference 0.6 mg/mmol

CI = confidence interval; eGFR = estimated glomerular filtration rate; mg = milligrams; mg/mmol = milligrams per millimole; mil/min*1.73 m^2 = milliliters per minute per 1.73 meters squared; NR = not reported

* Outcomes are actively ascertained unless otherwise noted.

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Six RCTs comparing metformin with a combination of metformin plus SGLT-2 inhibitor reported on albuminuria and eGFR (Table 113).[153, 165, 166, 168, 170, 267]

Two 102-week trials evaluated renal impairment or failure as a categorical outcome, with conflicting results.[170, 267] One found slightly more events of renal impairment in the metformin plus SGLT-2 inhibitor arm compared to metformin (3.3% vs. 0%),[267] and the other RCT did not find a clear pattern of differences across arms.[170] A 16-week RCT also evaluated renal impairment or failure events and reported similar rates of events across arms both arms.[168]

Three short-term trials evaluated eGFR and found no meaningful differences between the metformin and metformin plus SGLT-2 inhibitor arms.[165, 166, 168] One 12-week RCT compared metformin with metformin plus empagliflozin and stated qualitatively that treatment with empagliflozin did not significantly change creatinine clearance or urine albumin compared with metformin.[153] (SOE: Low; Neither favored)

Table 113. Randomized controlled trials comparing metformin with a combination of metformin plus an SGLT-2 inhibitor on impaired renal function

Author, Year	Followup	Definition of Impaired Renal Function*	Results
Rosenstock, 2013[153]	12 weeks	Creatinine clearance, microalbuminuria	NR for any arm Qualitative statement of no difference across groups
Schumm-Draeger, 2015[168]	16 weeks	Renal impairment/failure as specified in protocol	Metformin: 4/101 (4%) Metformin + dapagliflozin 5 mg twice daily: 3/100 (3%) Metformin + dapagliflozin 10 mg daily: 3/99 (3%)
Schumm-Draeger, 2015[168]	16 weeks	eGFR (ml/min/1.73 m^2)	Metformin vs. metformin + dapagliflozin 5 mg twice daily: between-group difference from baseline to final, 4.0 (95%CI, 1.6 to 4.4) Metformin vs. metformin + dapagliflozin 10 mg: between-group difference from baseline to final, 0.8 (95%CI, -1.5 to 4.1)
Haring, 2014[166]	24 weeks	eGFR (ml/min/1.73 m^2)	Metformin vs. metformin + empagliflozin 10 mg: between-group difference from baseline to final, 0.9 (95% CI, -1.5 to 3.3) Metformin vs. metformin + empagliflozin 25 mg: between-group difference from baseline to final, 2.7 (95% CI, 0.6 to 4.8)
Qiu, 2014[165]	18 weeks	eGFR	% reduction in eGFR Metformin: 0.3% Metformin + canagliflozin 50 mg twice daily: 0.7% Metformin + canagliflozin 150 mg twice daily: 3.8%
Bailey, 2013[170]	102 weeks	Renal impairment or failure, not otherwise specified	Metformin: 2/137 (1.5%) Metformin + dapagliflozin 5 mg: 4/137 (2.9%) Metformin + dapagliflozin 10 mg: 2/135 (1.5%)
Bolinder, 2014[267]	102 weeks	MedDRA definition of renal impairment, renal failure	Metformin: 0/91 (0%) Metformin + dapagliflozin 10 mg: 3/91 (3.3%)

CI = confidence interval; eGFR = estimated glomerular filtration rate; MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams; mil/min*1.73 m^2 = milliliters per minute per 1.73 meters squared; NR = not reported
* Outcomes are actively ascertained unless otherwise noted.

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Three RCTs with long-term followup compared the effects of metformin plus a sulfonylurea to metformin plus a SGLT-2 inhibitor on renal impairment or failure, changes in eGFR, and albuminuria (Table 114).[54, 200, 201] One 208-week trial evaluated reduced creatinine clearance and renal impairment and found similar rates of events between arms.[54] Three trials evaluated changes in eGFR and found no meaningful differences in eGFR changes across arms.[54, 200, 201] Two trials evaluated albuminuria and found no differences between arms.[200, 201] (SOE: Low; Neither favored)

Table 114. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor on impaired renal function

Author, Year	Followup	Definition of Impaired Renal Function*	Results	Notes
Leiter, 2015[201]	104 weeks	eGFR (ml/min/1.73 m^2)	Metformin + glimepiride vs. metformin + canagliflozin 100 mg: between-group difference from baseline to final, -2.4 (95%CI, -6.3 to 1.5) Metformin + glimepiride vs. metformin + canagliflozin 300 mg: between-group difference from baseline to final, -4.2 (95%CI, -8.1 to -0.3)	Subjects meeting eGFR withdrawal criteria: n=6 in glimepiride arm, n=5 in canagliflozin 100 mg arm, and n=6 for canagliflozin 300 mg arm Unclear if included in analysis
Ridderstrale, 2014[200]	104 weeks	eGFR (ml/min/1.73 m^2)	Metformin + glipizide vs. metformin + empagliflozin 25 mg; between-group difference, 3.5 (95% CI, 2.2 to 4.8)	
Del Prato, 2015[54]	208 weeks	MedDRA defined decreased eGFR	Metformin + glipizide: 4/408 (1.0 %) Metformin + dapagliflozin: 2/406 (0.5 %)	
Del Prato, 2015[54]	208 weeks	MedDRA defined reduced creatinine clearance	Metformin + glipizide: 13/408 (3.2 %) Metformin + dapagliflozin: 20/406 (4.9%)	
Del Prato, 2015[54]	208 weeks	MedDRA defined renal impairment	Metformin + glipizide: 11/408 (2.7 %) Metformin + dapagliflozin: 10/406 (2.5%)	
Leiter, 2015[201]	104 weeks	Renal failure leading to medication discontinuation	Metformin + glimepiride: NR Metformin + canagliflozin 100 mg: NR Metformin + canagliflozin 300 mg: 3/385 (0.6%)	
Leiter, 2015[201]	104 weeks	Urine albumin-to-creatinine ratio (mg/g)	Metformin + glimepiride vs. metformin + canagliflozin 100 mg: between-group difference, 13.9 mg/g Metformin plus glimepiride vs. metformin plus canagliflozin 300 mg: between-group difference, 16.1 mg/g	
Ridderstrale, 2014[200]	104 weeks	Urine albumin-to-creatinine ratio (mg/g)	Metformin + glimepiride vs. metformin + empagliflozin 25 mg: between-group difference, 1.9 mg/g (95% CI, -5.1 to 8.9 mg/g)	Subgroup with no albuminuria at baseline

CI = confidence interval; eGFR = estimated glomerular filtration rate; MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams; mg/g = milligrams per gram; mil/min*1.73 m^2 = milliliters per minute per 1.73 meters squared; NR = not reported

* Outcomes are actively ascertained unless otherwise noted.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Four RCTs compared metformin plus a DPP-4 inhibitor with metformin plus a SGLT-2 inhibitor on renal outcomes (Table 115).[90, 153, 158, 209] Three trials evaluated changes in eGFR and found no substantial differences across arms.[90, 158, 209] One 12-week RCT evaluated changes in creatinine clearance and microalbuminuria comparing metformin plus sitagliptin and metformin

plus empagliflozin and found no significant differences between arms.[153] (SOE: Low; Neither favored)

Table 115. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus an SGLT-2 inhibitor on impaired renal function

Author, Year	Followup	Definition of Impaired Renal Function*	Results
Ferrannini, 2013[90]	90 weeks	eGFR (ml/min/1.73 m^2)	Metformin + sitagliptin vs. metformin + empagliflozin 10 mg: between-group difference, 4.1 (95% CI, 0.3 to 8.6) Metformin + sitagliptin vs. metformin + empagliflozin 25 mg: between-group difference, 2.8 (95% CI, -1.5 to 7.1)
Lavalle-Gonzalez, 2013[158]	52 weeks	Decreased eGFR	Metformin + sitagliptin vs. metformin + canagliflozin 100 mg: between-group difference, 1.0% Metformin + sitagliptin vs. metformin + canagliflozin 300 mg: between-group difference, 0.9%
Rosenstock, 2013[153]	12 weeks	Creatinine clearance, microalbuminuria	NR for any arm Qualitative statement of no difference across groups
Rosenstock, 2015[209]	24 weeks	GFR decrease, not otherwise defined	Metformin + saxagliptin: 1/176 (0.6%) Metformin + dapagliflozin: 0/179 (0%)

CI = confidence interval; eGFR = estimated glomerular filtration rate; mg = milligrams; mil/min*1.73 m^2 = milliliters per minute per 1.73 meters squared; NR = not reported
* Outcomes are actively ascertained unless otherwise noted.

Strength of Evidence for Impaired Renal Function

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 116 and summarized in the key points. All studies were RCTs. Study limitations for all the comparisons were low or medium. The evidence was generally imprecise because of small event rates and sample sizes. In general, we did not find strong differences in outcomes in the lower- versus higher-quality studies. We did not find any evidence of publication bias in any of the comparisons for renal outcomes. We also did not find any evidence of publication bias or reporting bias in the grey literature review.

Table 116. Strength of evidence domains for monotherapy and metformin-based combination comparisons in terms of impaired renal function among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. SGLT-2 inhibitors	3 (1,456)	High	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
DPP-4 inhibitors vs. SGLT-2 inhibitors	2 (1,394)	Medium	Consistent	Direct	Precise	Undetected	Low	Neither favored
Metformin vs. metformin + SGLT-2 inhibitors	6 (2,340)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer studies)	3 (3,815)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	4 (2,972)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

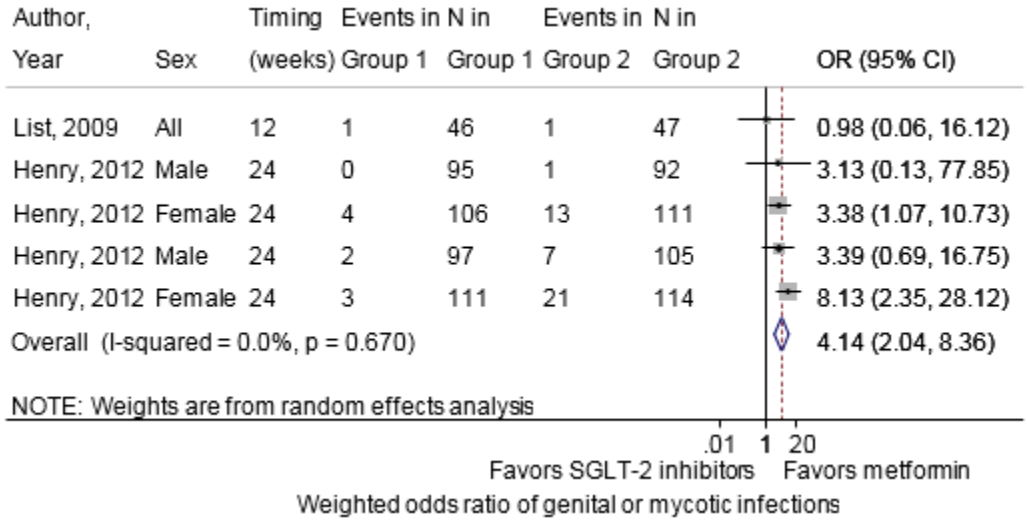
Evidence for Genital Mycotic Infections

Monotherapy Comparisons

Metformin Versus SGLT-2 Inhibitors

Three medium- to high-quality, short RCTs (reported in two articles) compared metformin with SGLT-2 inhibitors and found more genital infections in the SGLT-2 inhibitor vs. metformin arms (pooled OR, 4.1; 95% CI, 2.0 to 8.3) (Figure 91).[88, 89] ORs did appear to vary by gender. No single study markedly influenced the results, and we did not find significant statistical heterogeneity ($I^2 = 0.0\%$).

Figure 91. Pooled odds ratio of genital or mycotic infections comparing metformin with SGLT-2 inhibitors



CI = confidence interval; Group 1 = metformin; Group 2 = sodium-glucose co-transporter-2 inhibitors; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

We did not include a low-quality, 78-week RCT in the meta-analysis because of its longer duration.[90] This study compared metformin with empagliflozin and reported slightly higher rates of genital infections among females for SGLT-2 inhibitor therapy [1/28 (3.6%) with metformin versus 3/57 (5.3%) with metformin plus low-dose empagliflozin and 3/52 (5.8%) with metformin plus high-dose empagliflozin] and more genital infections among males with SGLT-2 inhibitors [0/28 (0%) with metformin versus 2/49 (4.1%) with metformin plus low dose empagliflozin and 3/57 (5.3%) with metformin plus high- dose empagliflozin]. (SOE: Moderate; Metformin favored)

DPP-4 Inhibitors Versus SGLT-2 Inhibitors

Two RCTs (24 to 26 weeks) compared outcomes from use of 100 mg of sitagliptin daily to an SGLT-2 inhibitor, by gender.[114, 240] Both trials reported higher rates of genital infections among both women and men with use of SGLT-2 inhibitors compared with sitagliptin, with

some of the comparisons statistically significant (Table 117).[114, 240] (SOE: Low; DPP-4 inhibitors favored)

Table 117. Randomized controlled trials comparing DPP-4 inhibitors with SGLT-2 inhibitors on genital infections

Author, Year	Medication Dose	Women Events/N (%)	Men Events/N (%)
Stenlof, 2014[240]	Sitagliptin 100 mg Canagliflozin 100 mg Canagliflozin 300 mg	1/155 (1.2) 3/170 (3) 3/170 (3.2)	0/155 (0) 3/170 (3) 5/170 (6.5)
Roden, 2013[114]	Sitagliptin 100 mg Empagliflozin 10 mg Empagliflozin 25 mg	1/82 (1) 3/82 (4) 7/79 (9)	1/141 (1) 4/142 (3) 2/144 (1)

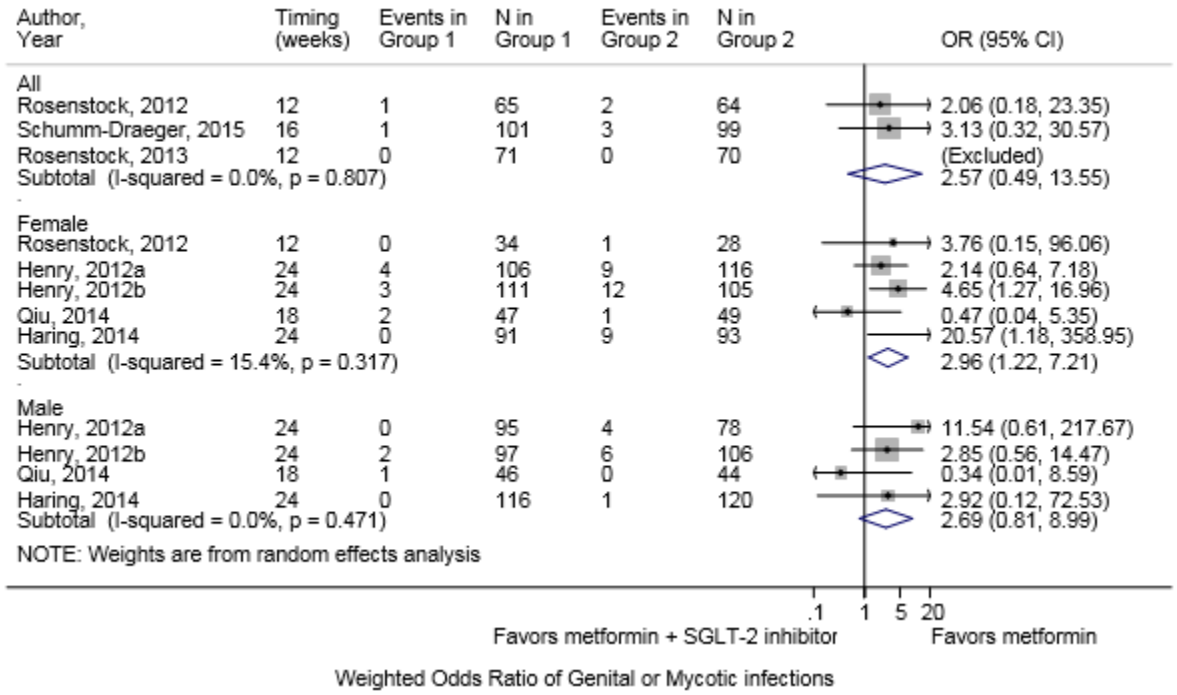
mg = milligrams

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Seven RCTs (reported in six articles) compared metformin with metformin plus a SGLT-2 inhibitor and found increased odds of genital infections for combination therapy over metformin monotherapy with no clear differences by gender: pooled OR, 3.0 (95% CI, 1.2 to 7.2) for women and pooled OR, 2.7 (95% CI, 0.8 to 9.0) for men (Figure 92).[88, 156, 165, 166, 168] No single study markedly influenced the results, and we did not find significant statistical heterogeneity (I^2 = 15.4% for women and I^2 = 0.0% for men). An additional 12-week RCT did not provide sex-stratified analyses so was not included in the meta-analysis.[153] This study reported more genital infection events in one of the groups receiving empagliflozin compared with the other two arms (metformin plus sitagliptin 100 mg: 0%; metformin plus empagliflozin 10 mg: 9.9%; metformin plus empagliflozin 25 mg: 0%).

Figure 92. Pooled odds ratio of genital or mycotic infections comparing metformin with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

We excluded two RCTs from the meta-analysis because of their longer durations.[170, 267] The results of those RCTs are included in Table 118 and are consistent with the findings from the short-term studies. (SOE: High; Metformin favored)

Table 118. Randomized controlled trials comparing metformin with a combination of metformin plus an SGLT-2 inhibitor on genital infections

Author, Year	Followup	Genital Infection Outcome*	Results (Metformin Versus Metformin + SGLT-2 Inhibitor)
Rosenstock, 2012[156]	12 weeks	Symptomatic of genital infections	Metformin: 1/65 (2%) Metformin + canagliflozin 100 mg: 4/64 (6%) Metformin + canagliflozin 200 mg: 2/65 (3%) Metformin + canagliflozin 300 mg: 2/64 (3%)
Rosenstock, 2013[153]	12 weeks	MedDRA definition	Metformin: 0% Metformin + empagliflozin 10 mg: 9.9% Metformin + empagliflozin 25 mg: 0%
Schumm-Draeger, 2015[168]	16 weeks	MedDRA definition	Metformin: 1/101 (1%) Metformin + dapagliflozin 5 mg twice daily: 5/100 (5%) Metformin + dapagliflozin 10 mg: 3/99 (3%)
Qiu, 2014[165]	18 weeks	Males: balanitis candida and genital infection fungal. Females: vaginal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis	Males Metformin: 1/46 (2.2%) Metformin + canagliflozin 100 mg: 1/40 (2.5%) Metformin + canagliflozin 300 mg: 0/44 (0%) Females Metformin: 2/47 (4.3%) Metformin + canagliflozin 100 mg: 6/53 (11.3%) Metformin + canagliflozin 300 mg: 1/49 (2.0%)
Henry, 2012 (a)[88]	24 weeks	Events suggestive of vulvovaginitis, balanitis, and related genital infection	Males Metformin: 0% Metformin + dapagliflozin 5 mg: 5.1% Females Metformin: 3.8% Metformin + dapagliflozin 5 mg: 7.8%
Haring, 2014[166]	24 weeks	MedDRA definition	Males Metformin: 0/116 (0%) Metformin + empagliflozin 10 mg: 1/125 (0.8%) Metformin + empagliflozin 25 mg: 1/120 (0.8%) Females Metformin: 0/91 (0%) Metformin + empagliflozin 10 mg: 7/92 (7.6%) Metformin + empagliflozin 25 mg: 9/93 (9.7%)
Henry, 2012 (b)[88]	24 weeks	Based on a predefined list of signs, symptoms and other events suggestive of genital infection	Males Metformin: 2/97 (2.1%) Metformin + dapagliflozin 10 mg: 6/106 (5.7%) Females Metformin: 3/111 (2.7%) Metformin + dapagliflozin 10 mg: 12/105 (11.4%)
Bolinder, 2014[267]	102 weeks	Genital infections	Metformin: 1/91 (1.1%) Metformin + dapagliflozin 10 mg: 2/91 (2.2%)
Bailey, 2013[170]	102 weeks	Events suggestive of genital infection	Metformin: 7/137 (5.1%) Metformin + dapagliflozin 2.5 mg: 16/137 (11.7%) Metformin + dapagliflozin 5 mg: 20/137 (14.6%) Metformin + dapagliflozin 10 mg: 17/135 (12.6%)

MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams
* Outcomes are actively ascertained unless otherwise noted.

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

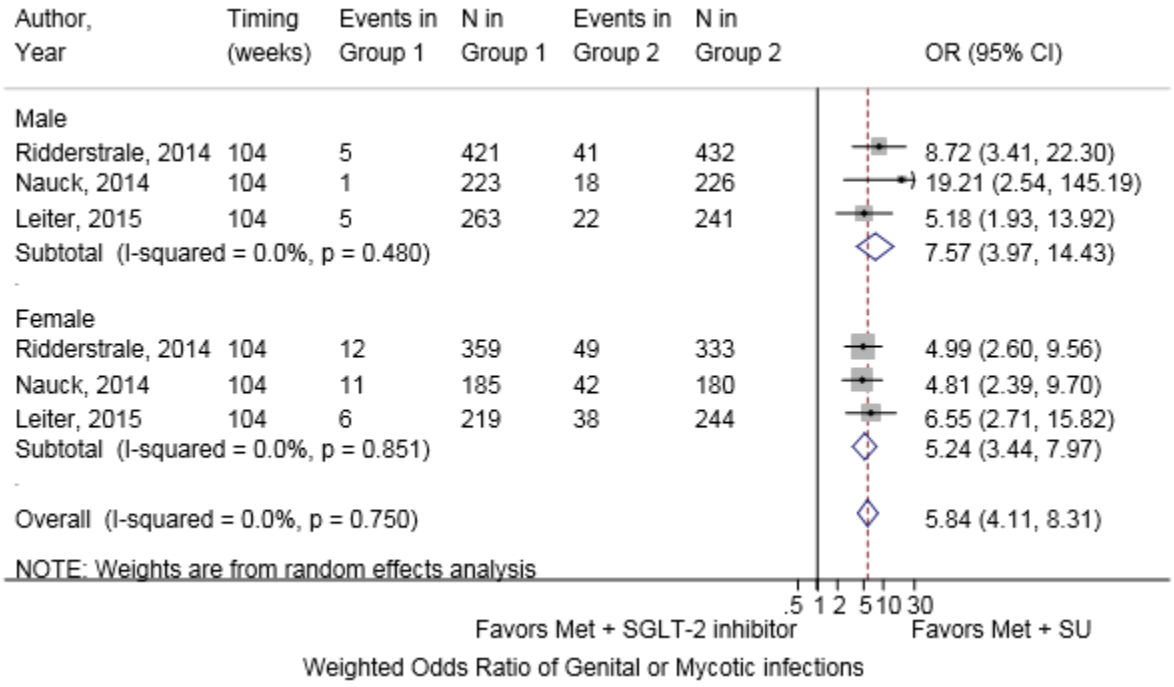
Three RCTs compared metformin plus a sulfonylurea with metformin plus a SGLT-2 inhibitor, suggesting increased odds of genital infections for metformin plus SGLT-2 inhibitors and differences in relative odds by gender: pooled OR, 5.2 (95% CI, 3.4 to 7.8) for women and pooled OR, 7.6 (95% CI, 4.0 to 14.4) for men (Figure 93).[200, 201, 219] No single study markedly influenced the results, and we did not find significant statistical heterogeneity (I^2 = 0.0% for women and I^2 = 0.0% for men). A 208-week extension of Nauck, 2014 et al.[219] also reported higher rates of genital infection in the SGLT-2 inhibitor combination arm and among women compared with men (Table 119).[54] Losses to followup were high (>60% in both arms).[54] (SOE: High; Combination of metformin plus a sulfonylurea favored)

Table 119. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor on genital infections

Author, Year	Definition	Medication Dose	Women Events/N (%)	Men Events/N (%)
Ridderstrale, 2014[200]	MedDRA definition of genital infection	Metformin + glimepiride Metformin + empagliflozin 25 mg	12/359 (3%) 49/333 (15%)	5/421 (1%) 41/432 (9%)
Leiter, 2015[201]	Males: balanitis, balanitis candida, balanoposthitis, genital candidiasis, genital infection fungal, and posthitis Females: genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis	Metformin + glimepiride Metformin + canagliflozin 300 mg	6/219 (2.7%) 38/244 (15.6%)	5/263 (1.9%) 22/241 (9.1%)
Nauck, 2014[219]	MedRA definition of genital infection	Metformin + glipizide Metformin + dapagliflozin	11/185 (5.9) 42/180 (23.3)	1/223 (0.4) 18/226 (8.0)
Del Prato, 2015[54]*	Confirmed genital infection	Metformin + glipizide Metformin + dapagliflozin	11/408 (5.9%) 41/406 (22.8%)	1/408 (0.4%) 17/406 (7.5%)

MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams
* Del Prato, 2015 is the 208-week extension study of Nauck, 2014.

Figure 93. Pooled odds ratio of genital or mycotic infections comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; Met = metformin; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2; SU = sulfonylurea

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Five RCTs compared metformin plus a DPP-4 inhibitor with metformin plus a SGLT-2 inhibitor and generally found more genital infections with the SGLT-2 inhibitor arms.[90, 153, 156, 158, 209] These studies were not pooled owing to differences in study duration. Two of the studies stratified outcomes by gender (Table 120).[90, 158] (SOE: Moderate; Combination of metformin plus a DPP-4 inhibitor favored)

Table 120. Randomized controlled trials comparing a combination of metformin plus a DPP-4 inhibitor with a combination of metformin plus an SGLT-2 inhibitor on genital infections

Author, Year	Followup (Weeks)	Medication Dose	Women Events/N (%)	Men Events/N (%)	Total Events/N (%)*	Comments
Rosenstock, 2012[156]	12 weeks	Metformin + sitagliptin	1/27 (3.7)	NR	NR	
		Metformin + canagliflozin 100 mg	2/28 (7.1)	NR	NR	
		Metformin + canagliflozin 200 mg	4/32 (12.5)	NR	NR	
		Metformin + canagliflozin 300 mg	1/28 (3.6)	NR	NR	
Rosenstock, 2013[153]	12 weeks	Metformin + sitagliptin	NR	NR	2/71 (2.8)	
		Metformin + empagliflozin 10 mg	NR	NR	7/71 (9.9)	
		Metformin + empagliflozin 25 mg	NR	NR	0/70 (0)	
Rosenstock, 2015[209]	24 weeks	Metformin + saxagliptin	NR	NR	1/176 (0.6)	
		Metformin + dapagliflozin 10 mg	NR	NR	10/179 (6.0)	
Lavalle-Gonzalez, 2013[158]	52 weeks	Metformin + sitagliptin	5/194 (2.6)	2/172 (1.2)	NR	ITT analysis not performed
		Metformin + canagliflozin 100 mg	22/194 (11.3)	9/174 (5.2)	NR	
		Metformin + canagliflozin 300 mg	20/202 (9.9)	4/165 (2.4)	NR	
Ferrannini, 2013[90]	78 weeks	Metformin + sitagliptin	0/29 (0)	0/27 (0)	NR	ITT analysis not performed
		Metformin + empagliflozin 10 mg	2/83 (2.4)	3/83 (3.6)	NR	
		Metformin + empagliflozin 25 mg	3/88 (3.4)	3/78 (3.8)	NR	

DPP-4 = dipeptidyl peptidase-4; ITT = intention-to-treat; mg = milligrams; NR = not reported; SGLT-2 = sodium-glucose co-transporter-2

* Results for both genders provided if sex-stratified results not reported

Strength of Evidence for Genital Mycotic Infections

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 121 and summarized in the key points. All studies were RCTs. Study limitations for all the comparisons were low or medium. In general, we did not find strong differences in outcomes in the lower- versus higher-quality studies. We did not find any evidence of publication bias in any of the comparisons for genital infections. We also did not find any evidence of publication bias or reporting bias in the grey literature review.

Table 121. Strength of evidence domains for monotherapy and metformin-based combination comparisons in terms of genital mycotic infections among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. SGLT-2 inhibitors	4 (2,292)	Medium	Consistent	Direct	Imprecise	Undetected	Moderate	Metformin favored; 4.1 (2.0 to 8.3) for SGLT-2 inhibitors vs. metformin
DPP-4 inhibitors vs. SGLT-2 inhibitors	2 (1,394)	Medium	Consistent	Direct	Imprecise	Undetected	Low	DPP-4 inhibitors favored
Metformin vs. metformin + SGLT-2 inhibitors	9 (4,035)	Low	Consistent	Direct	Precise	Undetected	High	Metformin favored; 3.0 (1.2 to 7.2) for females and 2.7 (0.8 to 9.0) for males
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer studies)	3 (3,815)	Medium	Consistent	Direct	Precise	Undetected	High	Metformin + SU favored; 5.2 (3.4 to 8.0) for females and 7.6 (4.0 to 14.4) for males
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	5 (3,423)	Medium	Consistent	Direct	Imprecise (n for metformin insufficient)	Undetected	Moderate	Metformin + DPP-4 inhibitors favored; range in OR, 1.0 to 10.4; range in RD, -3% to 9%

CI = confidence interval; DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; OR = odds ratio; RD = risk difference; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Fracture

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Three RCTs compared metformin with metformin plus an SGLT-2 inhibitor and found no differences in fractures.[168, 170, 267] Two of these had followup for longer than one year: One 102-week RCT compared metformin with metformin plus dapagliflozin and reported a slightly higher incidence of fractures in the highest-dose dapagliflozin arm [2/137 (1.5%) for metformin versus 2/137 (1.5%) for dapagliflozin 2.5 mg, 2/137 (1.5%) for dapagliflozin 5 mg, and 3/135 (2.2%) for dapagliflozin 10 mg]. There was a high loss to followup in this study, ranging from 30 percent to 47 percent across arms.[170] Another 102-week RCT compared metformin with metformin plus 10 mg of dapagliflozin and reported one fracture (1.1%) in each treatment arm (n=91 for both arms).[267] A single 16-week RCT compared metformin with metformin plus dapagliflozin and reported no fractures in either arm.[168] (SOE: Low; Neither favored for shorter studies; SOE: Low; Neither favored for longer studies)

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Two studies compared metformin plus a GLP-1 receptor agonist with metformin plus a SGLT-2 inhibitor, showing no differences in fracture risk.[200, 219] One 104-week RCT compared metformin plus glipizide with metformin plus dapagliflozin and showed a slightly higher incidence of fractures in the metformin plus glipizide arm [9/408 (2.2%) for metformin plus glipizide versus 6/406 (1.5%) for metformin plus dapagliflozin].[219] Another 104-week RCT compared metformin plus glimepiride to metformin plus empagliflozin showing similar incidences of fractures in both arms (2%).[200] (SOE: Insufficient)

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

One 24-week RCT compared metformin plus a DPP-4 inhibitor with metformin plus a SGLT-2 inhibitor and reported a slightly higher risk of fracture in the metformin arm [2/176 (1.0%) for metformin plus saxagliptin versus 1/179 (0.6%) for metformin plus dapagliflozin].[209] (SOE: Low; Metformin plus SGLT-2 inhibitor favored short-term fracture risk)

Strength of Evidence for Fracture

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 122 and summarized in the key points. All studies were RCTs. Study limitations for all the comparisons were low. We did not find any evidence of publication bias in any of the comparisons for fractures. A single 52-week, unpublished trial reported no fractures in either arm (NCT01368081), which is consistent with the other studies. We also did not find any evidence of publication bias or reporting bias in the grey literature review.

Table 122. Strength of evidence domains for monotherapy and metformin-based combination comparisons in terms of fracture among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. metformin + SGLT-2 inhibitors (shorter studies)	1 (200)	Low	Unknown	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + SGLT-2 inhibitors (longer studies)	2 (728)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer studies)	2 (2,363)	Medium	Inconsistent	Direct	Imprecise	Undetected	Insufficient	Unable to determine
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors (shorter study)	1 (534)	Low	Unknown	Direct	Imprecise	Undetected	Low	Metformin + SGLT-2 inhibitor favored

SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† We only include estimates for comparisons with high or moderate strength of evidence.

Evidence for Volume Depletion

Monotherapy Comparisons

Metformin Versus SGLT-2 Inhibitors

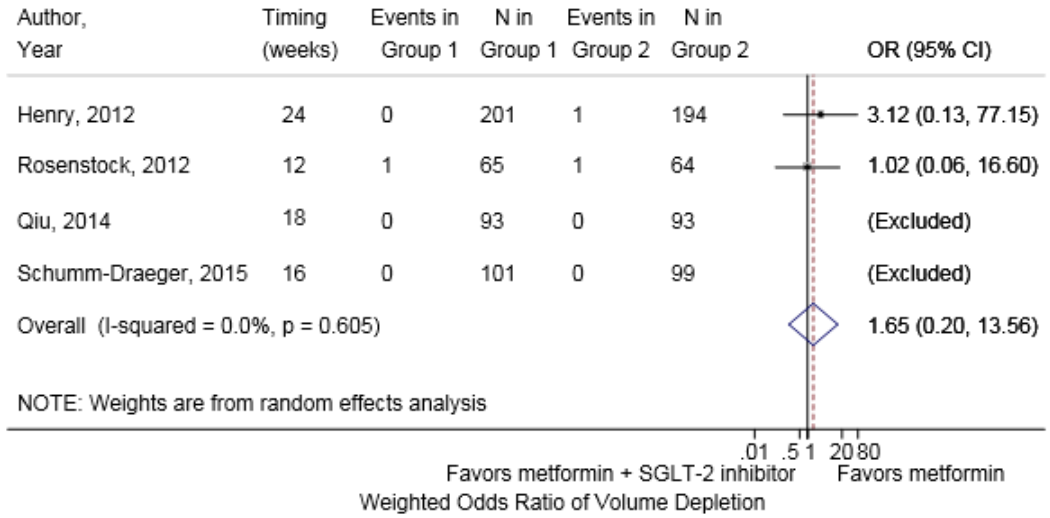
Two moderately-sized, short RCTs compared metformin with SGLT-2 inhibitors and reported inconsistent results.[88, 89] One 12-week RCT comparing metformin with dapagliflozin reported a higher incidence of hypotensive events with metformin (4% for metformin versus 0% for dapagliflozin 5 mg and 10 mg).[89] One 24-week RCT comparing metformin with dapagliflozin 5 mg reported significantly more events of hypotension or syncope with dapagliflozin [0/201 (0%) for metformin versus 4/203 (2%) for dapagliflozin 5 mg].[88] (SOE: Low; Conflicting results)

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Six RCTs compared metformin with the combination of metformin plus an SGLT-2 inhibitor for this outcome.[88, 156, 165, 168, 170, 267] We did not combine these in a meta-analysis because of differences in study duration and definition of volume depletion events (Table 123, Figure 94). The two RCTs with long-term followup had large losses to followup and were conflicting with one suggesting a higher risk of hypotension in the SGLT-2 inhibitor-based arm[267] and the other suggesting similar rates of volume depletion across arms.[170] Volume depletion events were rare in the four short-duration RCTs (Figure 94).[88, 156, 165, 168] (SOE: Low; Neither favored for shorter studies; SOE: Low; Neither Favored for longer studies)

Figure 94. Pooled odds ratio of volume depletion comparing metformin with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; Group 1 = metformin; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate. Studies were excluded because they did not contribute any events.

Table 123. Randomized controlled trials comparing metformin with a combination of metformin plus an SGLT-2 inhibitor on volume depletion

Author, Year	Followup	Definition of Volume Depletion Outcome	Results (Metformin Versus Metformin + SGLT2 Inhibitor)	Comments
Rosenstock, 2012[156]	12 weeks	Adverse events possibly related to hypovolemia (dizziness, dizziness postural, heart rate increased, tachycardia, and urine output decreased)	Metformin: 1/65 (2%) Metformin + canagliflozin 100 mg: 4/64 (6%) Metformin + canagliflozin 200 mg: 3/65 (5%) Metformin + canagliflozin 300 mg: 1/64 (2%)	Included in meta-analysis
Schumm-Draeger, 2015[168]	16 weeks	MedDRA definition for hypotension, dehydration, or hypovolemia	Metformin: 0/101 (0%) Metformin + dapagliflozin 5 mg twice daily: 0/100 (0%) Metformin + dapagliflozin 10 mg: 0/99 (0%)	Included in meta-analysis
Qiu, 2014[165]	18 weeks	Orthostatic hypotension, postural dizziness	Metformin: 0/93 (0%) Metformin + canagliflozin 100 mg: 0/93 (0%) Metformin + canagliflozin 300 mg: 0/93 (0%)	Included in meta-analysis
Henry, 2012[88]	24 weeks	Hypotension or syncope	Metformin: 0/201 (0%) Dapagliflozin 5 mg: 1/194 (0.5%)	No ITT analysis performed Included in meta-analysis
Bolinder, 2014[267]	102 weeks	Hypotension	Metformin: 0/91 (0%) Metformin + dapagliflozin 10 mg: 1/91 (1.1%)	Unclear if ITT analysis performed High losses to follow up
Bailey, 2013[170]	102 weeks	MedDRA definition for hypotension, dehydration, or hypovolemia	Metformin: 2/137 (1.5%) Metformin + dapagliflozin 2.5 mg: 0/137 (0%) Metformin + dapagliflozin 5 mg: 3/137 (2.2%) Metformin + dapagliflozin 10 mg: 2/135 (1.5%)	High losses to follow up

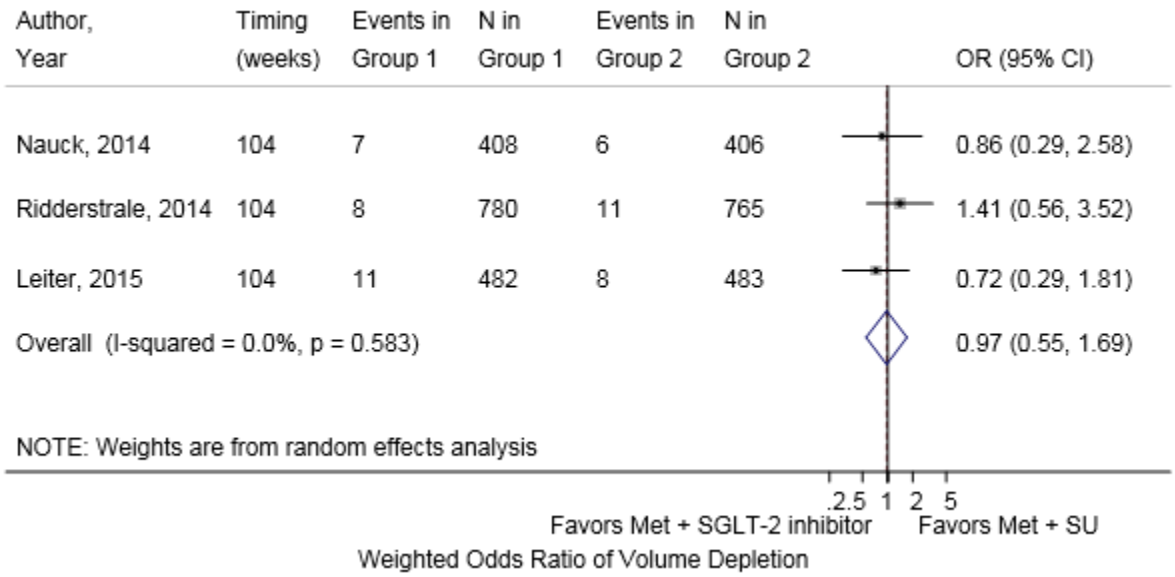
ITT = intention-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams; SGLT-2 = sodium-glucose co-transporter-2

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Three 104-week RCTs compared metformin plus a sulfonylurea to metformin plus a SGLT-2 inhibitor and described volume depletion events, with varying definitions in each study. The evidence suggested little difference between arms (pooled OR for metformin plus sulfonylurea versus metformin plus SGLT-2 inhibitor, 1.0; 95% CI, 0.6 to 1.7) (Figure 95 and Table 124).[200, 201, 219] No single study markedly influenced the results, and we did not detect substantial heterogeneity (I^2 = 0.0%). (SOE: Low; Neither favored)

Figure 95. Pooled odds ratio of volume depletion comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor



CI = confidence interval; Group 1 = combination of metformin plus a sulfonylurea; Group 2 = combination of metformin plus a sodium-glucose co-transporter-2 inhibitor; OR = odds ratio; SGLT-2 = sodium-glucose co-transporter-2
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Table 124. Randomized controlled trials comparing a combination of metformin plus a sulfonylurea with a combination of metformin plus an SGLT-2 inhibitor on volume depletion

Author, Year	Followup	Definition of Volume Depletion Outcome	Results Events/N (%)
Leiter, 2015[201]	104 weeks	Decreased blood pressure, dehydration, postural dizziness, hypotension, orthostatic hypotension, presyncope, and syncope	Metformin + glimepiride: 11/482 (2.3%) Metformin + canagliflozin 100 mg: 8/483 (1.7%) Metformin + canagliflozin 300 mg: 12/485 (2.5%)
Ridderstrale, 2014[200]	104 weeks	MedDRA definition	Metformin + glimepiride: 8/780 (1%) Metformin + empagliflozin 25 mg: 11/765 (1%)
Nauck, 2014[219]	104 weeks	Hypotension, dehydration, hypovolemia	Metformin + glipizide: 7/408 (1.7%) Metformin + dapagliflozin 10 mg: 6/406 (1.5%)

MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus an SGLT-2 Inhibitor

Two RCTs compared metformin plus a DPP-4 inhibitor with metformin plus a SGLT-2 inhibitor and showed no clear differences in volume depletion outcomes.[156, 158] Both studies reported active ascertainment of the outcome. One 52-week RCT comparing metformin plus sitagliptin with metformin plus canagliflozin 100 mg and 300 mg reported similar incidences in orthostatic hypotension (0% to 0.3% across all three arms).[158] One 12-week RCT comparing metformin plus sitagliptin with metformin plus canagliflozin reported slightly more events related to hypovolemia in the arms receiving the lower doses of canagliflozin [1/65 (2%) for

metformin plus sitagliptin versus 4/64 (6%) for metformin plus canagliflozin 100 mg, 3/65 (5%) for metformin plus canagliflozin 200 mg, and 1/64 (2%) for metformin plus canagliflozin 300 mg].[156] (SOE: Low; Neither favored)

Strength of Evidence for Volume Depletion

The strength of evidence for the comparative effects of monotherapy and metformin-based combinations are presented in Table 125 and summarized in the key points. All studies were RCTs. Study limitations for all the comparisons were low. Where quality influences results, we describe that under the appropriate comparisons. In general, we did not find strong differences in outcomes in the lower- versus higher-quality studies. We did not find any evidence of publication bias in any of the comparisons for volume depletion. We also did not find any evidence of publication bias or reporting bias in the grey literature review.

Table 125. Strength of evidence domains for monotherapy and metformin-based combination comparisons in terms of volume depletion among adults with type 2 diabetes

Comparison*	Number of Studies (Subjects)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence	Summary†
Metformin vs. SGLT-2 inhibitors	2 (992)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Conflicting results from 2 RCTs
Metformin vs. metformin + SGLT-2 inhibitors (shorter studies)	4 (1533)	Medium	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin vs. metformin + SGLT-2 inhibitors (longer studies)	2 (728)	Low	Consistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer studies)	3 (3,815)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	2 (1,735)	Medium	Inconsistent	Direct	Imprecise	Undetected	Low	Neither favored

DPP-4 inhibitors = dipeptidyl-peptidase 4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide-1 agonists; SGLT-2 inhibitors = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione

* We only list comparisons that were evaluated by at least one randomized controlled trial. All other comparisons were considered to have insufficient evidence because of a lack of available evidence. Unless otherwise specified, conclusions for the intermediate outcomes are short-term (1 year or shorter) because there are few longer-duration studies evaluating this outcome.

† Unless otherwise specified, the estimates are the pooled odds ratios (95 percent confidence intervals) from randomized controlled trials. We only include estimates for comparisons with high or moderate strength of evidence.

Key Question 4: Subgroups

Although thirty-two studies reported on the comparative effectiveness and safety for sub-populations relevant to Key Question 4 (Appendix D, Table D14), few studies had sufficient power to assess comparative effectiveness or safety by subgroup. The evidence favoring one medication over another across subgroups is unclear.

We included 29 RCTs and five cohort studies that addressed this Key Question. The majority of these trials (n=22) evaluated subgroup effects on the outcome of HbA1c.[54, 77, 80, 82, 84, 104, 107, 118, 126, 139, 141, 142, 145, 149, 151, 154, 160, 193 41187, 194, 241, 268, 269] RCTs also included subgroup results on weight gain,[77, 169, 241, 270, 271] hypoglycemia,[190, 195, 272] and fractures.[273] The cohort studies included subgroup results for mortality,[234] cardiovascular events,[245, 246] fractures,[274] and kidney disease progression.[249]

We were unable to draw conclusions about the differential effects of medications in the specified sub-populations because of the small number of studies available for any one outcome for the included comparisons.

Subgroups Defined by Age

Hemoglobin A1c

Sixteen RCTs, out of the 21 reporting on subgroups for this outcome, did not find differences in the effects of diabetes medications on HbA1c by age.

Cardiovascular Mortality and Morbidity

We included two retrospective cohort studies which reported on cardiovascular outcomes by age. One study compared metformin users, glimepiride users, and glyburide users.[245] Metformin use was associated with lower risk of nonfatal CVD events compared with glyburide use among older participants (>51 years old) (Adjusted HR for metformin vs. glyburide among those age 51 to 70 years, 0.28; 95% CI, 0.20 to 0.39; adjusted HR among those age 71 years or older, 0.30; 95% CI, 0.18 to 0.48). In the younger age group, only metformin was associated with a decreased risk of cardiovascular events (adjusted HR for metformin vs. glyburide, 0.39; 95% CI, 0.21 to 0.73). Another retrospective cohort study compared metformin with sulfonylureas and found no difference in the incidence of death or cardiovascular events across age groups.[246]

Hypoglycemia

Two RCTs evaluating the risk of hypoglycemia by age reported no differences by age for the combination of metformin and a sulfonylurea versus the combination of metformin and a DPP-4 inhibitor.[190, 195]

Kidney Function Decline

A retrospective cohort study compared the effect of metformin, rosiglitazone and sulfonylureas on kidney function and found no differences by age for kidney disease progression.[249]

Subgroups Defined by Sex

Hemoglobin A1c

Seventeen RCTs examined the impact of sex on glycemic control (HbA1c) for the comparisons of interest and found no differences by sex.[77, 80, 82, 84, 104, 107, 118, 126, 139, 141, 142, 145, 149, 151, 154, 194, 268]

Weight

One trial reported a greater weight reduction among men compared with women for the combination of metformin plus dapagliflozin versus metformin; the mean decrease at 24 weeks attributable to the addition of dapagliflozin was 2.76 kg for men and 1.22 kg for women, p for interaction = 0.048).[169] A second study comparing metformin with pioglitazone reported that while both men and women in the metformin arm had a slight but not significant weight loss, those in the pioglitazone arm differentially gained weight; the mean increase at 12 weeks was 1.78 kg for women (p = 0.039) and 0.86 kg for men (p=0.151).[77] Another trial that compared metformin with metformin plus pioglitazone over 24 weeks reported no treatment differences by sex.[270]

Long-Term Clinical Outcomes

The two retrospective cohort studies described above comparing the effect of metformin and different sulfonylureas on cardiovascular risk found no association between treatments and cardiovascular outcomes by sex.[245, 246] However, a retrospective cohort study of new monotherapy users found that compared with those on metformin, women on rosiglitazone had a higher risk of death (RR, 6.21; 95% CI, 1.22 to 19.65) than men (RR, 1.76; 95% CI, 1.41 to 2.18).[234] The p-value for the interaction between treatment and sex was 0.034.

Hypoglycemia

Two studies that compared the combination of metformin and sulfonylureas with the combination of metformin and a DPP-4 inhibitor found no differences by gender for this outcome.[190, 272]

Fractures

A retrospective analysis of the ADOPT trial found that women treated with rosiglitazone had an increased risk of fracture relative to those treated with metformin or glyburide (HR, 1.57 and 1.61, respectively); the investigators did not find an increased risk of fracture among men in this study with a median of 4 years of followup.[273] One cohort study reported that women have a higher risk of peripheral fractures when treated with pioglitazone than with sulfonylureas (adjusted HR, 1.77; 95% CI, 1.32 to 2.38).[274] However, the study did not find a statistically significant increased risk of peripheral fractures for women treated with rosiglitazone compared with sulfonylureas (adjusted HR, 1.17; 95% CI 0.91 to 1.50). Men treated with thiazolidinediones had an increased risk compared with men treated with sulfonylureas (adjusted HR, 1.61; 95% CI, 1.18 to 2.20).

Subgroups Defined by Race/Ethnicity

Hemoglobin A1c

Thirteen RCTs examined the impact of race on HbA1c reduction, and found no differences by race for the comparisons studied.[82, 84, 104, 107, 126, 139, 141, 145, 151, 154, 160, 194]

Kidney Function Decline

A single retrospective cohort evaluating the effects of metformin, glyburide, and glimepiride on progression of chronic kidney disease found no differences by race for this outcome.[249]

Subgroups Defined by Body Mass Index

Hemoglobin A1c

Sixteen RCTs found no differences by baseline BMI on the effects of diabetes medications on HbA1c reduction for the comparisons studied.[54, 80, 82, 84, 104, 107, 118, 126, 139, 141, 145, 154, 194, 241, 269]

Weight

Two studies reported on effects of weight in a subgroup of obese patients, but they did not report on this outcome in the non-obese patients.[241, 271] One RCT found that obese patients treated with metformin lost an average of 1.3 kg, but those treated with sulfonylureas gained an average of 3.7 kg.[271] In another RCT, obese patients allocated to metformin lost an average of 0.9 kg but those allocated to a combination of metformin plus rosiglitazone gained an average of 2.5 kg.[241]

Discussion

This systematic review addresses the comparative effectiveness and safety of diabetes medications used most frequently in the United States as monotherapy and compares therapies in combination with metformin to each other. This review updates and adds to two previous comparative effectiveness reviews (CER) published in 2007[15] and 2011,[16] by focusing on the head-to-head comparisons of medications most relevant to clinicians and their patients (Table 2), particularly those for which evidence was previously lacking. We broadened the scope by including seven medications newly approved by Food and Drug Administration (FDA), including one new medication class, the sodium-glucose co-transporter-2 (SGLT-2) inhibitors. We identified 107 new studies, which included 87 trials and 20 observational studies, published since we completed our 2011 review. Our comprehensive review of the newer medication classes in comparison with other medications and comparisons of combination therapies is an important contribution to the literature, because it is the first to address this many comparisons for a wide range of outcomes in patients with type 2 diabetes mellitus.

Key Findings in Context

Intermediate Outcomes

One hundred sixty-two RCTs evaluated the intermediate outcomes of hemoglobin A1c (HbA1c), weight, systolic blood pressure, and heart rate. Studies mainly measured these intermediate outcomes at 1 year or less; only six studies were longer than 2 years. The few longer studies had results consistent with the results from the shorter-term studies. Rarely, results from a longer study conflicted with results from a short-term study, but the high losses to followup (generally >20%) made these uninterpretable. Therefore, short-term results are discussed below, unless otherwise specified in the figure or text.

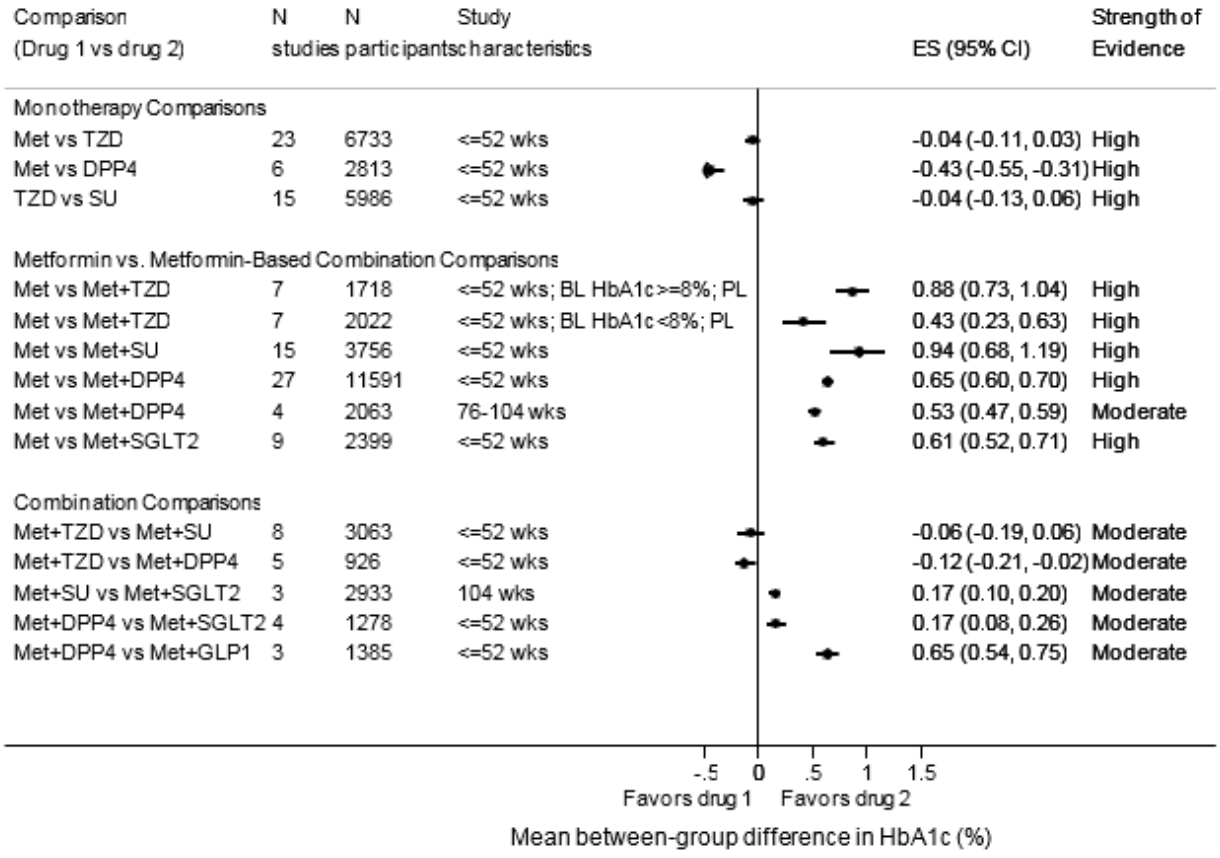
Hemoglobin A1c

HbA1c is unequivocally linked to microvascular disease,[10, 275, 276] making it a good proximal outcome to measure. Consistent with the prior 2011 report,[16] most oral diabetes medications (thiazolidinediones, sulfonylureas, and metformin) had similar efficacy in reducing HbA1c when used as monotherapy (Figure 96). The one exception was that metformin yielded a greater reduction in HbA1c compared with DPP-4 inhibitors, consistent with the prior report.[16] In the last report,[16] metformin versus sulfonylurea was graded as having a high strength of evidence showing no significant between-group differences in HbA1c; therefore, it was not updated in this report. In this report, metformin versus GLP-1 receptor agonists and metformin versus SGLT-2 inhibitors also showed no clear between-group differences in HbA1c. They were graded as low strength of evidence, because the three studies in each comparison were imprecise and inconsistent. In this update, we found inconsistent findings in the studies of GLP-1 receptor agonists. It may be that the individual GLP-1 receptor agonists have different effects on HbA1c. A 2011 Cochrane systematic review showed small between-group differences in HbA1c, around 0.3%, for different GLP-1 receptor agonists.[277] The strength of evidence was graded as insufficient for the other monotherapy comparisons of SGLT-2 inhibitors and GLP-1 receptor agonists, and this warrants further study.

All metformin combination therapies were better at reducing HbA1c than metformin monotherapy regimens, with between-group differences of around 0.7 to 1 absolute percentage

points (Figure 96). While several moderate strength of evidence combination comparisons were significantly favored over the comparator combination (Figure 96), most between-group differences were small (<0.3%), with questionable clinical relevance. Only one combination comparison with moderate strength of evidence was favored by >0.3% over any other combination comparison: the combination of metformin plus a GLP-1 receptor agonist reduced HbA1c more than metformin plus a DPP-4 inhibitor. Despite the clinical interest in comparing metformin plus injectables, there was insufficient or low strength of evidence on glycemic control for the following comparisons: metformin plus the GLP-1 receptor agonists versus metformin plus basal or premixed insulin, and metformin plus premixed insulin versus metformin plus basal insulin. Two prior network meta-analyses[278, 279] showed that most metformin-based combination comparisons had similar reductions in HbA1c. However, the results of the direct comparisons evaluated in this report are more precise allowing us to detect smaller between group differences than the results of the indirect comparisons found in the network meta-analyses.

Figure 96. Pooled between-group differences in hemoglobin A1c and strength of evidence for monotherapy and metformin-based combination comparisons



BL = baseline; CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (mean between-group difference in HbA1c); GLP1 = glucagon-like peptide-1 agonists; HbA1c = hemoglobin A1c; Met = metformin; PLE = profile likelihood estimate; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione; wks = weeks

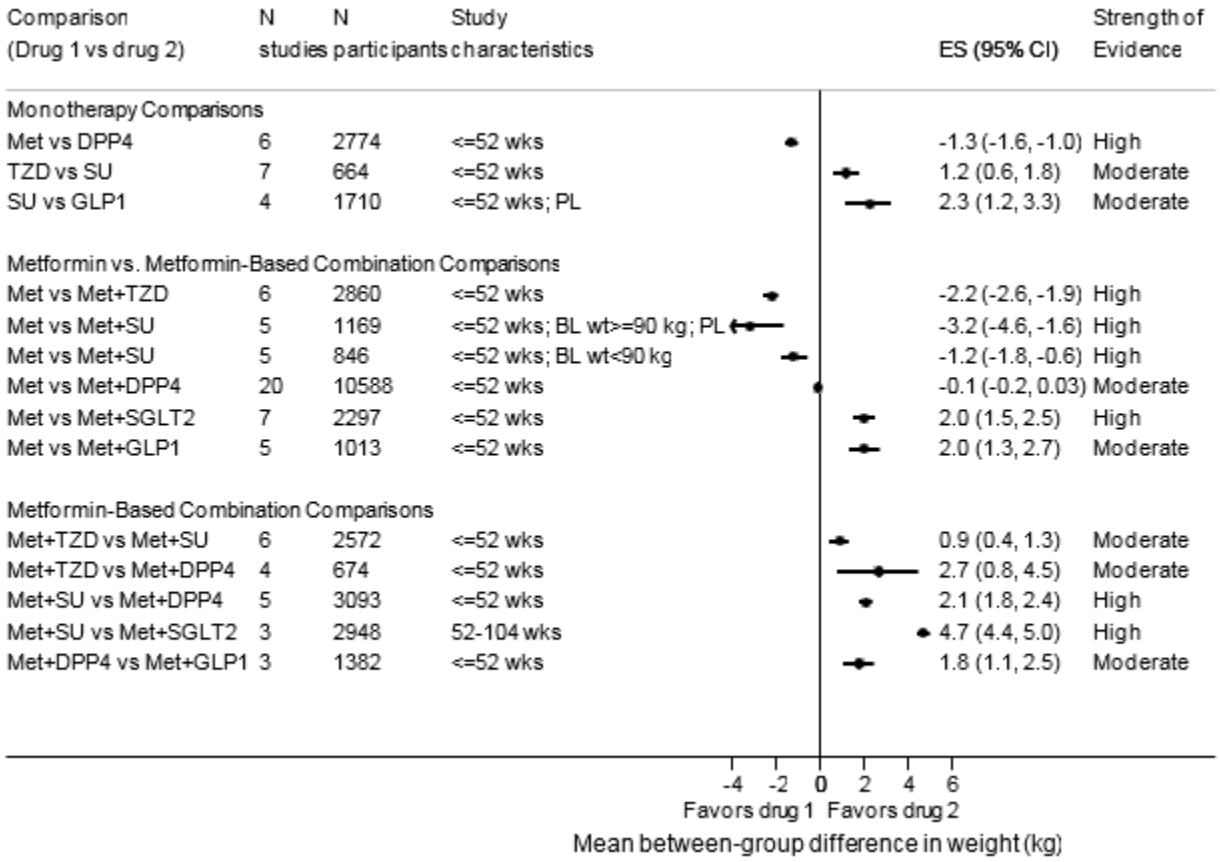
The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis.

Weight

Monotherapy and combination medication comparisons generally showed significant between-group differences when comparing medications anticipated to increase weight (sulfonylurea, thiazolidinediones, and insulin) with medications expected to maintain or decrease weight (metformin, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors) (Figure 97). In the prior report, metformin versus thiazolidinediones and metformin versus sulfonylureas were found to favor metformin, with differences of 2.5 kg, with high strength of evidence; therefore, these comparisons were not updated. In this report, metformin decreased weight more than DPP-4 inhibitors, while sulfonylureas caused slightly less weight gain than thiazolidinediones (Figure 97). Compared with metformin plus a DPP-4 inhibitor, the combinations of metformin plus GLP-1 receptor agonists and metformin plus SGLT-2 inhibitors were favored (Figure 97). Several comparisons discussed below had moderate strength of evidence but were unable to be pooled owing to differences among the studies. SGLT-2 inhibitors decreased weight more than metformin and more than DPP-4 inhibitors (between-group differences ranging from -1.3 kg to -2.7 kg). DPP-4 inhibitors and GLP-1 receptor agonists both decreased weight more than thiazolidinediones (between-group differences ranging from -2.3 kg to -3.5 kg). Lastly, metformin plus a sulfonylurea was favored over metformin plus a premixed or long-acting insulin (between-group difference ranging from -0.5 kg to -1.7 kg). Despite the clinical interest in comparing metformin plus injectables, there was low strength of evidence on weight for the comparisons of metformin plus the GLP-1 receptor agonists versus metformin plus basal or premixed insulin and metformin plus premixed insulin versus metformin plus basal insulin.

Notably, weight differences were small to moderate in these mainly short trials. However, even small to moderate amounts of weight gain (5 percent to 10 percent of body weight) may be associated with increased insulin resistance.[280] In addition, weight loss and glycemic control were reported as the primary drivers of patient preferences for diabetes medications when compared with treatment burden and side effects in a recent systematic review.[281] Drug effects on weight, therefore, have a strong impact on the choice of the drug added for second-line combination therapy in a patient not well controlled on a single agent. Our findings about diabetes medications effects on weight are similar to other prior systematic reviews.[16, 277, 282] As monotherapy and in combination with metformin, thiazolidinediones, sulfonylureas, and basal or premixed insulin are associated with weight gain; DPP-4 inhibitors with weight maintenance; and SGLT-2 inhibitors and GLP-1 receptor agonists with weight loss.[16, 277, 282, 283] Our systematic review builds on prior work by adding more direct comparative data about metformin combinations, which further confirm the known weight effects of the individual medications.

Figure 97. Pooled between-group differences in weight and strength of evidence for monotherapy and metformin-based combination comparisons



BL = baseline; CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; ES = effect size (mean between-group difference in weight); GLP1 = glucagon-like peptide-1 agonists; kg = kilograms; Met = metformin; PLE = profile likelihood estimate; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione; wks = weeks; wt = weight

The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis.

Systolic Blood Pressure and Heart Rate

Systolic blood pressure and heart rate were evaluated for the newer classes of medications, SGLT-2 inhibitors and GLP-1 receptor agonists, owing to suspected effects of these medications based on prior literature.[277, 282] Blood pressure control is important in adults with diabetes.[220, 284-286] The United Kingdom Prospective Diabetes Study (UKPDS) showed that for every 10 mmHg decrease in systolic blood pressure, there is a 15 percent decrease in diabetes-related deaths.[285] Consistent with a prior systematic review on SGLT-2 inhibitors,[282] the SGLT-2 inhibitors consistently reduced systolic blood pressure in all comparisons where there were sufficient studies (significant between-group differences of 3 to 5 mmHg when compared with other diabetes medications that have no effect on blood pressure). Our review builds on this work by evaluating direct comparisons of specific medication classes as comparators, as opposed to grouping all active comparators together. This is especially important, because thiazolidinediones and GLP-1 receptor agonists also have been associated with decreases in systolic blood pressure by 3 to 5 mmHg.[15, 277] Metformin plus a GLP-1 receptor agonist had a greater reduction in systolic blood pressure compared with metformin alone (pooled between-group difference, 3.1 mmHg; 95% CI, 1.4 to 4.9 mmHg), with moderate strength of evidence.

While the clinical relevance of these small differences is unclear, a change of 3-5 mmHg is about half the effect of a low sodium diet (around 7-11 mmHg) and about one-third the effect of blood pressure medications (around 10-15 mmHg).[287, 288] Future research will be needed to determine whether there are any links between these small differences in blood pressure and micro- and macrovascular outcomes, given the prevalent use of effective medications to reduce cardiovascular risk (e.g., aspirin, blood pressure, and cholesterol medications).

Increased heart rate is associated with increased mortality.[289] However, whether heart rate is an independent predictor of long-term clinical outcomes such as mortality is less clear.[44] We opted to evaluate heart rate for the newer medications, SGLT-2 inhibitors and GLP-1 receptor agonists, given their association with mortality. In addition, we wanted to see if the benefits from blood pressure reduction might be offset by a concomitant increase in heart rate. We did not identify any prior systematic reviews that have evaluated this outcome for the diabetes comparisons of interest. Only two comparisons had sufficient data to grade the evidence as more than insufficient or low. The SGLT-2 inhibitors in combination with metformin were found to decrease heart rate by 1.5 bpm (95% CI, 0.6 bpm to 2.3 bpm) when compared with metformin plus a sulfonylurea; metformin and GLP-1 receptor agonist trials showed no between-group differences in heart rate. Therefore, these early findings support the findings of minimal to no effects on heart rate and no increase in heart rate for the newer medications.

All-Cause Mortality and Macrovascular and Microvascular Outcomes

Ninety-six RCTs and 22 observational studies evaluated these clinical outcomes. Compared to the prior report,[16] the evidence on mortality, cardiovascular mortality, and cardiovascular morbidity was strengthened for many comparisons, although most of this evidence was of low strength. The evidence regarding treatment effect on microvascular outcomes remains largely insufficient. Overall, the evidence base on these outcomes was limited by the short duration of RCTs (<2 years) and a lack of high-quality observational studies that would allow detection of treatment differences for infrequent outcomes. Also, none of the included RCTs were designed to evaluate these long-term outcomes.

All-Cause Mortality, Cardiovascular Mortality, and Cardiovascular Morbidity

This report builds on our prior results for the comparison of metformin and sulfonylurea monotherapy.[16] In this update, we found moderate strength of evidence that sulfonylurea monotherapy was associated with a 50 percent to 70 percent increased relative risk (absolute risk difference, 0.1% to 2.9% in RCTs; number needed to treat, 34 to 1,000) of long-term cardiovascular mortality compared with metformin monotherapy. Our findings on all-cause mortality and cardiovascular morbidity were supportive of this conclusion, with low strength of evidence suggesting that metformin is favored over sulfonylurea monotherapy for both long-term mortality and cardiovascular morbidity. Our findings on sulfonylurea monotherapy enhance findings from meta-analyses published in 2012 and 2013, which relied more heavily on observational data or did not report explicitly on head-to-head comparisons of metformin and sulfonylurea monotherapy.[290, 291] Importantly, we cannot know the absolute impact of individual drug classes on cardiovascular outcomes from this comparative effectiveness analysis. Our results suggest that cardiovascular mortality is lower in the metformin than sulfonylurea arms of the studies; however, we do not know if metformin actually decreases cardiovascular mortality

or just increases cardiovascular mortality less than sulfonylureas, and likewise, we do not know if sulfonylureas actually increase cardiovascular mortality or just decrease cardiovascular mortality less than metformin.

We evaluated pioglitazone and rosiglitazone separately when they were compared with other drug classes for all-cause mortality and cardiovascular outcomes, given concerns about cardiovascular risk and mortality associated with rosiglitazone raised previously[292] and acted upon by the FDA through recommendations regarding the prescription of this medication in 2010.[293, 294] While the strength of evidence was low, metformin was favored over the combination of metformin plus rosiglitazone for short-term all-cause mortality, as well as cardiovascular mortality and cardiovascular morbidity; metformin was also favored, albeit with low strength of evidence, over rosiglitazone monotherapy for long-term mortality and long-term cardiovascular morbidity.

We had little evidence on the combination of metformin plus a sulfonylurea or metformin plus a thiazolidinedione. In The Rosiglitazone Evaluated for Cardiovascular Outcomes in oral agent combination therapy for type 2 Diabetes (RECORD) trial, 4,447 participants with diabetes were randomized to a rosiglitazone-based combination (with either metformin or sulfonylurea) or to the combination of metformin plus a sulfonylurea.[49] We excluded this study from this outcome assessment, because it did not stratify results by a comparison of interest. This trial did not find a difference between rosiglitazone-based two-drug therapy and metformin plus a sulfonylurea for the primary endpoint, cardiovascular hospitalization or death. After 5.5 years, all-cause mortality, cardiovascular death, and stroke were slightly higher in the metformin plus sulfonylurea arm, and myocardial infarction rates were slightly (non-statistically significantly) higher in the rosiglitazone combination therapy arm. Of note, the FDA commissioned an independent re-adjudication and analysis of the data from RECORD and subsequently (in 2013) lifted their restrictions on rosiglitazone usage.[295]

Although strength of evidence was low, compared with the combination of metformin plus a sulfonylurea, the combination of metformin plus a DPP-4 inhibitor was associated with lower rates of long-term all-cause mortality and cardiovascular mortality and morbidity; an unpublished study with long-term followup was supportive of these conclusions. We also identified many new studies evaluating short-term all-cause mortality and cardiovascular outcomes for DPP-4 inhibitor comparisons, but most of this evidence was of low strength.

Several meta-analyses published since the 2011 report have evaluated DPP-4 inhibitors and all-cause mortality and cardiovascular outcomes; they tended to combine comparators (active, placebo, or both) against DPP-4 inhibitors so were not conclusive about specific direct comparisons.[296-301] The conclusions of these reviews have been based mainly on trials with less than 2 years of followup and have reported mixed results on short-term mortality and cardiovascular risk.

Outside of these meta-analyses, three large RCTs have evaluated DPP-4 inhibitors compared with placebo, added to the standard diabetes treatment per routine clinical care, and cardiovascular outcomes.[302-304] None of these RCTs evaluated direct head-to-head comparisons of interest, and none were included in this review. All of these trials designated a composite cardiovascular outcome as the primary outcome and reported non-inferiority (but not superiority) for the DPP-4 inhibitor addition compared with placebo addition for the composite cardiovascular outcome.[302-304] Rates of the primary endpoint were lower in the DPP-4 inhibitor versus placebo arm in two of the three trials [risk difference (statistical comparison not provided): -0.5%,[303] -0.2%,[302] 0.1%[302]]. Participants in all three trials were treated per clinical

standards with diabetes and cardiovascular medications, and, in the two trials reporting on this, participants in the placebo arm were more likely to have an increase or addition of a diabetes medication and were more likely to start insulin.[302, 303] There are several reasons that these RCTs demonstrating "non-inferiority" must be interpreted with caution: 1) differential diabetes medication use in the DPP-4 versus placebo arms raises the undeniable possibility that we are observing the effects of other diabetes medications (e.g., insulin) on the cardiovascular outcomes; 2) the assumptions for the non-inferiority sample size/power calculations are based on relative measures when an absolute risk difference may be quite relevant (e.g., an absolute risk difference of 0.1% corresponds to a number needed to harm of 1,000 – a number that has public health relevance given the potential population to be exposed); 3) effects of DPP-4 inhibitors versus placebo on individual outcomes (e.g., mortality, cardiovascular mortality) varied across the studies (Table 126); and 4) followup times of the studies were still short relative to the likely duration of use in actual clinical populations.

Table 126. Placebo-controlled RCTs evaluating DPP-4 inhibitors added to standard treatment with composite cardiovascular primary outcome

Trial	N	Study Population	Median Followup	All-Cause Mortality	CVD Death	Nonfatal MI
SAVOR-TIMI 53[302]	16,492	CVD or risk factors	2.1 years	HR, 1.11 (0.96 to 1.27; *P*=0.15) RD: 0.3%	HR, 1.03 (0.87 to 1.22; *P*=0.72) RD: 0.3%	HR, 0.95 (0.80 to 1.12; *P*=0.52) RD: -0.2%
EXAMINE[304]	5,380	Recent CVD*	18 months	HR, 0.88 (0.71 to 1.09; P=0.23) RD: -0.8%	HR, 0.85 (0.66 to 1.10; P=0.21) RD: -0.8%	HR, 1.08 (0.88 to 1.33); P=0.47) RD: 0.4%
TECOS[303]	14,671	CVD	3.0 years	HR, 1.01 (0.90 to 1.14; *P*=0.88) RD: 0.2%	HR, 1.03 (0.89 to 1.19; P=0.71) RD: 0.2%	HR, NR RD: 0.1%

CVD = cardiovascular disease; EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; HR = hazards ratio; MI = myocardial infarction; RD = risk difference; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin
HR displayed with 95% CI and *P* value and RD with placebo arm as reference.
*Acute myocardial infarction or unstable angina in the past 15-90 days.

The evidence remains largely insufficient or of low strength regarding mortality and cardiovascular benefits or harms associated with GLP-1 receptor agonists. A meta-analysis suggested no difference in mortality rates for GLP-1 receptor agonists compared with other agents but did not make explicit monotherapy or combination comparisons.[305]

The evidence on all-cause mortality and cardiovascular mortality and morbidity for SGLT-2 inhibitor comparisons was limited. A meta-analysis of 25 studies comparing SGLT-2 inhibitor monotherapy with placebo or active monotherapy reported a non-statistically significant decrease in the risk of cardiovascular events for SGLT-2 inhibitors versus placebo or active monotherapy (OR, 0.90; 95% CI, 0.72 to 1.13); most studies were 52 weeks or shorter in duration.[282]

Retinopathy, Nephropathy, and Neuropathy

While we found more evidence on microvascular outcomes compared to the 2011 report,[16] all evidence was of low strength or inconclusive, thereby limiting substantial conclusions. We

did not identify any other evidence syntheses of these microvascular outcomes published since the prior report.

Adverse Events

One hundred thirty-seven RCTs and eight observational studies evaluated adverse events. The RCTs mainly measured adverse events at 1 year or earlier. Five percent of RCTs were longer than 2 years. Of the few RCTs that evaluated longer time frames, most (75%) had at least 20 percent losses to followup, making it challenging to draw firm longer-term conclusions. Therefore, results discussed below are generally for the short term (less than 2 years) unless otherwise specified in the figure or text. As adverse events sometimes accrue over time, the mainly short-term differences in adverse events could be larger in the long-term. In addition, short-term studies measuring rare adverse events with no between-group differences could develop between-group differences when evaluated over the longer term or in those with higher baseline risk.

Hypoglycemia

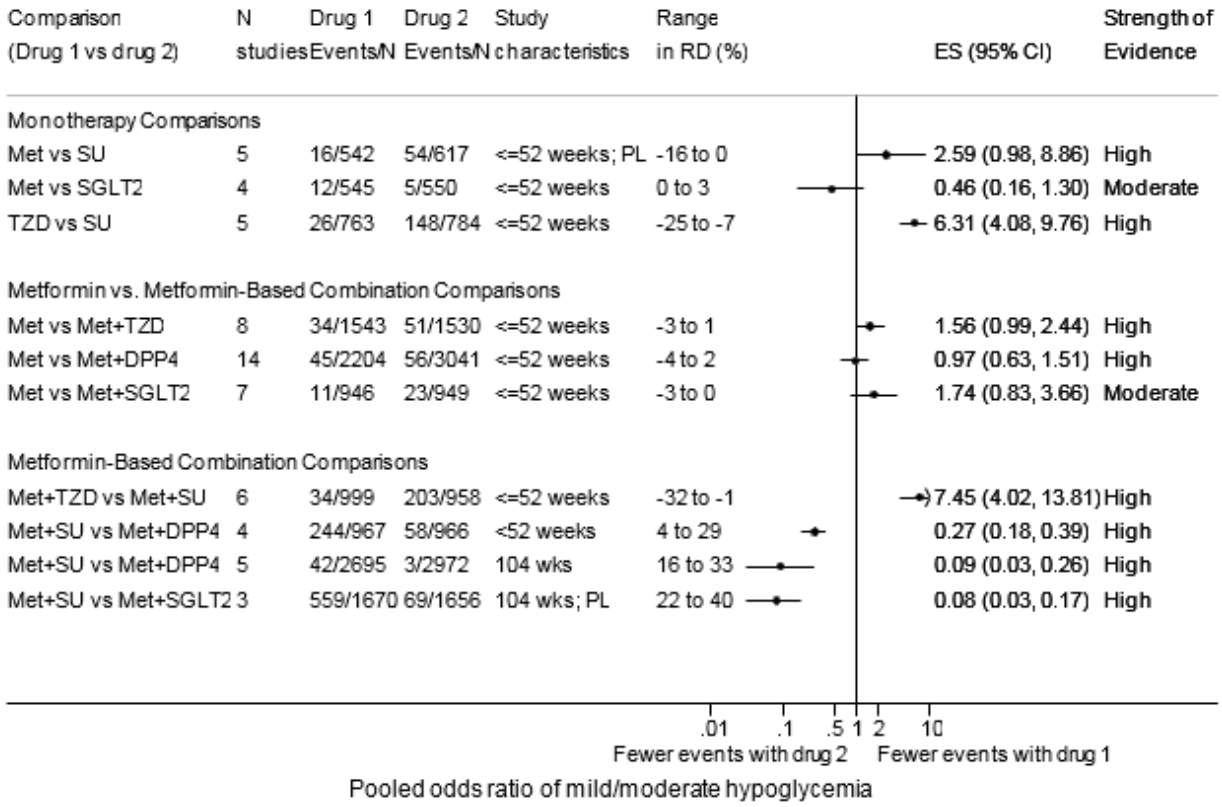
Severe hypoglycemia is associated with increased morbidity (e.g., reduced cognition), increased avoidable health care use (e.g., emergency room visits for hypoglycemia), and increased mortality in clinical trials and observational studies.[11, 306-308] We added new information on this important outcome in this report. We found moderate strength of evidence that sulfonylureas had an increased risk of severe hypoglycemia when compared with metformin (for RCTs: range in ORs, 1.4 to 2.0; range in RDs, 1% to 23%) or thiazolidinedione monotherapy (OR 8.1, RD, 0.5% from ADOPT).[50] Similarly, in combination with metformin, sulfonylurea use had a greater risk of severe hypoglycemia when compared with the combination of metformin plus DPP-4 inhibitors or SGLT-2 inhibitors (for RCTs: range in ORs, 6 to 14; range in RDs, 0% to 3%).

In this report, we confirmed the elevated risk of mild, moderate, or total hypoglycemia associated with sulfonylureas, either alone or in combination, compared with both the older and newer hypoglycemic agents (Figure 98). Of the combination comparisons, we confirmed that metformin plus basal insulin had an 11 percent to 77 percent lower risk of hypoglycemia compared with the combination of metformin plus premixed insulin, with moderate strength of evidence.

For the newer medications (SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors), we added to the evidence base by showing that SGLT-2 inhibitor monotherapy may be associated with 54 percent lower odds of mild or moderate hypoglycemia compared with metformin monotherapy, although absolute event rates were small across arms. This is consistent with a high-quality systematic review of the SGLT-2 inhibitors that also showed a non-significant lower risk of hypoglycemia in the SGLT-2 inhibitor arms compared with active comparators, although excluding sulfonylureas.[282] We found that mild or moderate hypoglycemia was 1.7-fold higher for the combination of metformin plus an SGLT-2 inhibitor compared with metformin monotherapy. We also found an increased risk of hypoglycemia with the combination of metformin plus premixed or basal insulin compared with metformin plus GLP-1 receptor agonists (range in absolute risk differences of 3% to 13%; moderate strength of evidence). Prior systematic reviews of individual classes of newer agents had sparse data on hypoglycemia when compared with active comparators, although the newer classes were generally found to have low rates of hypoglycemia.[277, 282, 298] While we found more studies

comparing metformin combinations with metformin plus sulfonylurea, there were still few studies on the newer medication classes as monotherapy and in combination with metformin.

Figure 98. Pooled odds ratios of mild/moderate hypoglycemia and strength of evidence for monotherapy and metformin-based combination comparisons



CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; Met = metformin; OR = odds ratio; PLE = profile likelihood estimate; RD = absolute risk difference; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinediones; wks = weeks

The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis. Drug 1 is the reference group.

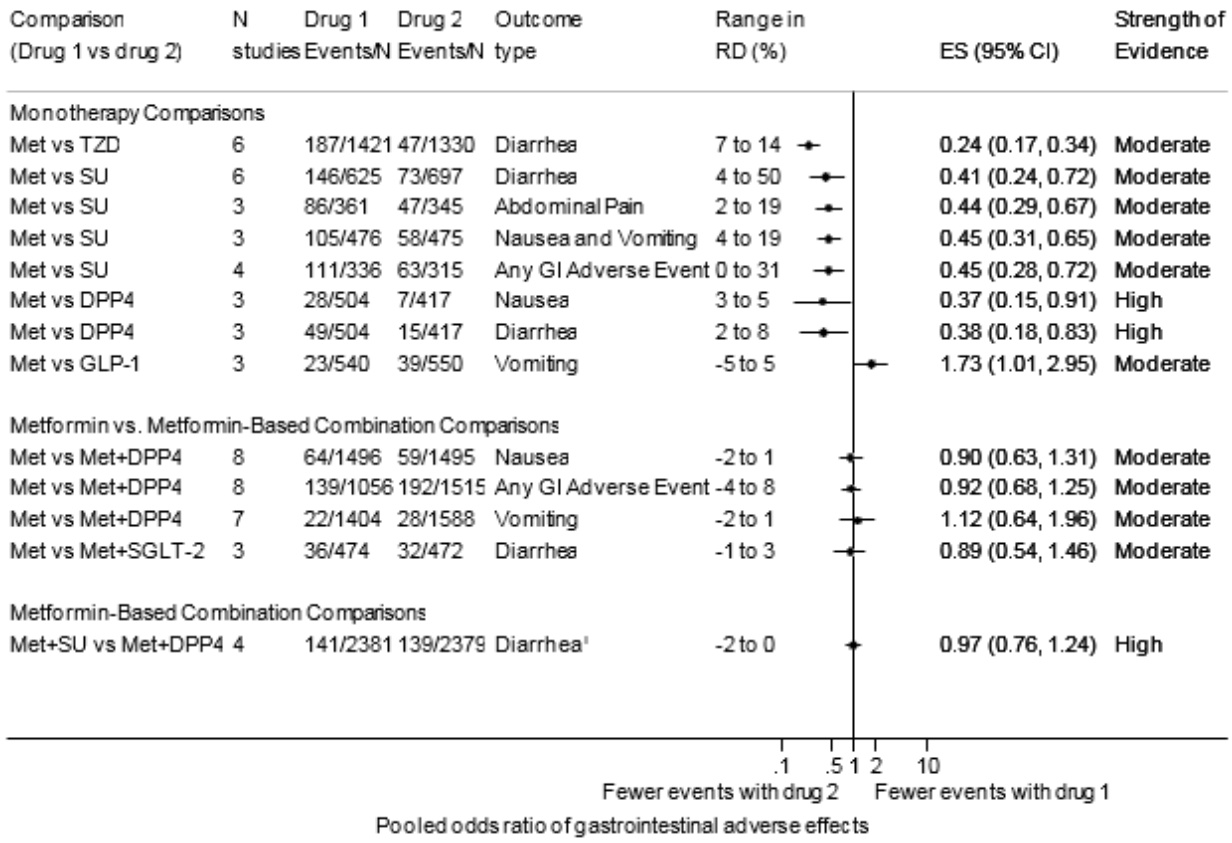
Gastrointestinal Side Effects

Metformin and GLP-1 receptor agonists as monotherapy and in combination had an increased risk of gastrointestinal (GI) adverse events (typically nausea, vomiting, or diarrhea) when compared with most other comparators, with moderate to high strength of evidence (Figure 99). Several medications had similar rates of GI adverse events with moderate or high strength of evidence: thiazolidinedione versus sulfonylurea, metformin plus a sulfonylurea versus metformin plus a DPP-4 inhibitor, metformin plus a thiazolidinedione versus metformin plus a sulfonylurea, metformin plus a sulfonylurea versus metformin plus a SGLT-2 inhibitor, metformin monotherapy versus metformin plus a SGLT-2 inhibitor, and metformin monotherapy versus metformin plus a DPP-4 inhibitor.

We confirmed findings of the 2011 report[16] showing that metformin had a greater risk of GI adverse events than thiazolidinediones, sulfonylureas, or DPP-4 inhibitors. We also report new findings showing GLP-1 receptor agonists have higher risk of GI adverse events when compared with thiazolidinediones and sulfonylureas, both as monotherapy or when used in combination with metformin. Our data confirm the GLP-1 comparative findings from a prior Cochrane

systematic review[277] and add information about specific combination comparisons and specific types of GI adverse events. GLP-1 receptor agonists also had higher risk of nausea and vomiting than metformin but no significant difference in diarrhea. The combinations of metformin plus DPP-4 inhibitors did not have worse GI adverse events than metformin monotherapy or metformin combinations. Lastly, we report new findings that SGLT-2 inhibitors showed no difference in GI adverse events when compared in combination with metformin against metformin plus sulfonylureas or compared with metformin monotherapy.

Figure 99. Pooled odds ratios of gastrointestinal adverse events and strength of evidence for monotherapy and metformin-based combination comparisons*



AE = adverse event; CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; GI = gastrointestinal; Met = metformin; OR = odds ratio; PLE = profile likelihood estimate; RD = absolute risk difference; SGLT2 = sodium-glucose co-transporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinediones

The width of the horizontal lines represents the 95 percent confidence intervals for each pooled analysis. Drug 1 is the reference group.

* All results presented in this graph are based on short-term (less than 52 weeks) studies unless otherwise specified.

† Based on studies with 104 weeks of followup.

Cancer

The evidence about cancer was generally insufficient because of a lack of studies, and the existing evidence was of low strength. Of 25 RCTs reporting on cancer, only eight (32 percent) had at least 2 years of followup. Most published studies for the comparisons did not report on cancer events in all arms, which limited our ability to synthesize the evidence quantitatively and to draw conclusions.

Reviews and meta-analyses published since the 2011 report suggest that metformin decreases the risk of many types of cancer[309, 310] and suggest that pioglitazone[311] increases the risk of bladder cancer slightly, but we did not include many of the studies supporting those conclusions because of our stringent inclusion criteria for observational studies. We excluded the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study,[312] because it did not evaluate a comparison of interest. This trial found a higher rate of bladder cancer in the pioglitazone versus placebo arm, which did not persist in the 5.8-year followup study that included only 74 percent of the original study population, most of whom did not take pioglitazone after the randomized period.[313]

However, our review adds low strength of evidence for many comparisons of GLP-1 receptor agonists and DPP-4 inhibitors. Evidence on these therapies and cancer outcomes is of particular interest given the preclinical evidence linking incretins (the GLP-1 receptor agonists and DPP-4 inhibitors) to cancer.[314] The three large, placebo-controlled RCTs described above, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction (SAVOR TIMI 53), Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE), and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), did not find an increased risk of cancer for DPP-4 inhibitors added to standard therapy.[302-304] The FDA prescribing information for the GLP-1 receptor agonists, liraglutide,[315] albiglutide,[316] exenatide,[317] and dulaglutide[318] includes a warning regarding the potential for a link between these agents and medullary thyroid cancer, based on data in mice and rats.[319] The evidence that we identified on the incretin-based therapies and cancer was of low strength and inconsistent. However, we found low strength of evidence that the combination of metformin plus a sulfonylurea was favored over the combination of metformin plus a DPP-4 inhibitor for longer-term cancer risk. An unpublished study's results, as well as longer-term followup of one of the included published studies,[141] were consistent with this finding and may have increased this evidence to moderate strength.

Congestive Heart Failure

There was only one long-term 4-year RCT and only a few observational studies of medium quality with 6 to 8 years of followup that could provide a comparative assessment of the safety of diabetes medications on congestive heart failure. We found low strength of evidence of 1.2 to 1.6 increased odds of heart failure with the thiazolidinedione class of medications, when compared with sulfonylureas or metformin. Our strength of evidence on this outcome dropped to low in this update (from moderate in the prior review), because we excluded lower-quality observational studies and also excluded the RECORD trial for this outcome, owing to the active comparator being *either* sulfonylurea or metformin, instead of a single active comparator. RECORD showed that the combination of thiazolidinediones and another agent (sulfonylurea or metformin) was associated with a significant doubling in the risk of heart failure in comparison with the combination of sulfonylurea and metformin (61/2220 versus 29/2227, risk ratio (RR), 2.1; 95% CI, 1.35 to 3.27).[49] These results showing a higher risk of congestive heart failure with thiazolidinediones were also confirmed in two recent meta-analyses.[320, 321] Both thiazolidinediones, rosiglitazone and pioglitazone, are contraindicated in patients with serious or severe heart failure (Stage 3 or Stage 4), according to product labels.[322, 323]

We had low or insufficient strength of evidence for most other medication comparisons for heart failure, including the newer agents. Despite recent concerns about congestive heart failure with DPP-4 inhibitors, we found low or insufficient strength of evidence on the comparative

safety of this drug class for this outcome in mainly short duration studies [five short duration RCTs reporting no events in the DPP-4 inhibitor arms, one short duration RCT with one event in the metformin plus DPP-4 arm and none in the comparator arm, and one RCT which reported few congestive heart failure events in the metformin plus DPP-4 inhibitor arm compared with the metformin plus sulfonylurea arm (three versus six respectively)]. Several large, double-blind, placebo-controlled RCTs evaluating DPP-4 inhibitors on cardiovascular outcomes in adults with moderate to high cardiovascular risk were excluded from our systematic review of head-to-head comparisons but deserve mention due to recent controversy.[302, 303, 324] Two of these RCTs (comparing either saxagliptin or alogliptin with placebo) reported a small increased risk of hospitalization for congestive heart failure in adults at moderate to high cardiovascular risk (between-group absolute risk differences of 0.7% and 0.9%).[302, 324] The EXAMINE trial with the alogliptin comparison reported these differences solely for the outcome of first hospitalization for heart failure in adults without pre-existing congestive heart failure as part of a *posthoc* subgroup analysis.[324] The third placebo-controlled RCT[303] compared sitagliptin with placebo on cardiovascular outcomes and reported no between-group differences in hospitalization for congestive heart failure. It is unclear if differences in these trials were due to differences in drug type, chance, or other causes. Due to these findings, however, the FDA has requested additional labeling for saxagliptin and alogliptin to reflect concerns of the potential increased risk of hospitalization for congestive heart failure.[325] Further research directly comparing DPP-4 inhibitors with other active comparators on heart failure outcomes will be useful in determining the comparative safety of these medications on heart failure risk, including results of two RCTs [the Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) and the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) studies] of linagliptin, which are in progress.[326, 327]

Liver Injury

Similar to the 2011 report, we found little evidence on liver injury. Compared to the prior report showing no between-group differences in liver injury, we downgraded the available evidence for metformin versus thiazolidinedione monotherapy (from moderate to low) and downgraded the evidence for thiazolidinedione versus sulfonylurea monotherapy (from high to low). Notably, there are FDA warnings of post-marketing cases of hepatic failure for both alogliptin[328] and pioglitazone,[329] but we found low or insufficient strength of evidence for thiazolidinedione- and DPP-4 inhibitor-based comparisons and liver injury.

Lactic Acidosis

Prior evidence on the elevated risk of lactic acidosis with phenformin, an earlier biguanide, and case reports of lactic acidosis among metformin users have led to continued concern about an increased risk of lactic acidosis with metformin; however, for most of the ~300 case reports on metformin and lactic acidosis, other factors contributing to lactic acidosis could not be excluded (e.g., acute myocardial infarction[330, 331] or acute kidney failure). Consistent with the prior report[16] and a Cochrane review on this topic,[332] we did not find an increased risk of lactic acidosis with metformin based on the little evidence identified. A more recent systematic review by Inzucchi et al.[333] evaluated the risk of lactic acidosis associated with metformin use in adults with mild to moderate chronic kidney disease (CKD; estimated glomerular filtration rates of 30-60 mL/min per 1.73 m^2). Using data from 65 studies (mainly observational), they reported an

overall incidence of 3-10 per 100,000 person-years of lactic acidosis in metformin users across studies,[333] which is similar to the background prevalence in adults with diabetes not on metformin.[332] The FDA is currently reviewing two citizen petitions to expand the use of metformin to adults with diabetes and mild to moderate CKD, with potential dose reductions in metformin to enhance safety in these populations.

Pancreatitis

Compared to the prior report, we identified many more studies on pancreatitis but found low strength of evidence for most comparisons. The DPP-4 inhibitors and GLP-1 receptor agonists were of most interest for this outcome, given the spontaneous reports to the FDA of pancreatitis associated with these agents. In the three large, placebo-controlled RCTs described above (SAVOR TIMI 53, EXAMINE, TECOS),[302-304] more cases of pancreatitis have been observed in the DPP-4 inhibitor than placebo arms with a consistent absolute risk difference of 0.1 percent (number needed to harm of 1,000). In the SAVOR TIMI 53 trial, definite acute pancreatitis occurred in 17 participants (0.2 percent) in the saxagliptin arm and nine participants (0.1 percent) in the placebo arm (P =0.17).[302] In EXAMINE, acute pancreatitis occurred in 12 participants (0.4 percent) in the alogliptin arm and in eight participants (0.3 percent) in the placebo arm. Finally, in TECOS, acute pancreatitis occurred in 23 participants (0.3 percent) and in 12 participants (0.2 percent) in the sitagliptin and placebo arms, respectively (HR, 1.93; 95% CI, 0.96 to 3.88; P =0.07). We excluded some of the Liraglutide Effect and Action in Diabetes (LEAD) RCTs from this report, because they did not evaluate comparisons of interest;[334] seven participants exposed to liraglutide and one exposed to a sulfonylurea were diagnosed with pancreatitis across the six LEAD trials.[335]

Systematic reviews of RCTs[336] and observational studies[337] have reported small, non-statistically significant increases in the relative odds of pancreatitis for incretin-based therapies versus control treatments. However, these meta-analyses are underpowered for this rare outcome, grouped GLP-1 receptor agonists and DPP-4 inhibitors together, grouped comparators (placebo and different active treatments), and included studies of patients without diabetes.

Severe Allergic Reactions

In the prior report, we did not find evidence on severe allergic reactions. However, the issue of hypersensitivity reactions with diabetes medications has become more prominent with the uptake of DPP-4 inhibitors[338] and GLP-1 receptor agonists.[339-341] In March, 2012, the FDA added a warning about the risk of hypersensitivity reactions with DPP-4 inhibitors.[342] Although still of low strength, we found the strongest evidence (based on four RCTs) that the addition of a DPP-4 inhibitor to metformin increases the risk of hypersensitivity reactions over metformin monotherapy alone. Prior data on the risk of hypersensitivity reactions with DPP-4 inhibitors have been mixed.[338] The SAVOR-TIMI 53 trial found similar rates of hypersensitivity reactions for saxagliptin compared with placebo.[302] In EXAMINE, angioedema was more frequent for the alogliptin arm (17/2701, 0.6%) than for the placebo arm (13/2679, 0.5%).[304] TECOS did not report on this outcome.[303]

Macular Edema and Decreased Vision

We did not find conclusive evidence on outcomes of macular edema and decreased vision. A concern regarding the risks of macular edema with the thiazolidinediones persists and is based primarily on observational studies.[343-345] Seven compared with three participants in the

rosiglitazone and active comparator arms, respectively, developed macular edema in the RECORD trial (described above), although there were more than 2000 treated in each arm.[49]

Adverse Events Specific to SGLT-2 Inhibitors

Our findings of an increased risk of genital mycotic infections for SGLT-2 inhibitors compared to other agents are consistent with recent reviews of this topic.[282, 346] The existing systematic reviews did not evaluate comparative effectiveness but, instead, grouped comparators together for synthesis.

In contrast to one of these recent systematic reviews of SGLT-2 monotherapy,[282] but consistent with another,[346] we did not find an increased risk of urinary tract infection (except for low strength of evidence in women for SGLT-2 inhibitor monotherapy relative to DPP-4 inhibitors) or volume depletion events; of note, all evidence in this report was of low strength (or insufficient) for urinary tract infection and volume depletion.

We also evaluated fracture risk and renal insufficiency associated with SGLT-2 inhibitors, given the issues raised about these adverse events in Vasilakou et al. 2013; in that review, the authors did not make conclusions about these outcomes, as their data were limited. We did not identify substantial evidence on these outcomes either. However, on September 10, 2015, the FDA strengthened its warning of an increased risk of fractures with canagliflozin based on pooled data from nine clinical trials.[347] The risk of fracture was increased for canagliflozin (1.4/100 patient-years and 1.5/100 patient-years for canagliflozin 100 mg and canagliflozin 300 mg respectively) versus the comparator (1.1/100 patient-years for placebo and active comparators combined) with a mean follow up of 85 weeks across trials. The labeling for canagliflozin notes that clinicians should consider factors that increase fracture when starting canagliflozin.[348]

The FDA issued a warning regarding the risk of ketoacidosis with SGLT-2 inhibitors on May 15, 2015.[325] We did not evaluate this outcome, as it was not a concern at the time that we selected outcomes for this report. The FDA warning stemmed from the observation of 20 cases of ketoacidosis in patients taking SGLT-2 inhibitors recorded in the FDA Adverse Event Reporting System (FAERS) database through June 6, 2014, followed by continued reports of ketoacidosis in patients taking SGLT-2 inhibitors since that time. A recent analysis of 17,596 participants from randomized trials of canagliflozin (mainly placebo-controlled), with 24,000 patient-years of exposure, demonstrated a higher number of patients experiencing ketoacidosis in the canagliflozin versus comparator arms: canagliflozin 100 mg: 4 (0.07 percent); canagliflozin 300 mg: 6 (0.11 percent); and comparator: 2 (0.03 percent).[349] The authors noted that six of the 10 patients with ketoacidosis in the canagliflozin arms were found to have type 1 diabetes, latent autoimmune diabetes of adulthood (LADA) or antibodies to GAD65.[349] The FDA has not changed labeling of the SGLT-2 inhibitors, at this time.[325]

Subgroups

The limited evidence on outcomes in subgroups was for the outcome of HbA1c and did not show differential effects of the included comparisons on glycemic control by age, sex, race/ethnicity, or body mass index. Otherwise, the evidence on the comparative effectiveness of diabetes medications in subgroups defined by age, sex, race/ethnicity, and body mass index was generally inconclusive. This is especially unfortunate for the age and race/ethnicity sub-populations because of the known disparities in diabetes prevalence and diabetes outcomes for these groups. Older Americans suffer disproportionately from diabetes, with over 25 percent of

persons 65 years of age and older having diabetes compared to 16 percent of persons 45 years of age to 64 years of age, and there is concern about the safety of medications (and polypharmacy) in older adults.[1, 8] Also, compared to non-Hispanic white adults in the United States, diabetes is 20 percent more common in Asian Americans, 70 percent more common in Hispanics and non-Hispanic blacks, and twice as common in American Indians/Alaska Natives.[1] Racial and ethnic minorities are also more likely to suffer from diabetes complications, including diabetic end-stage renal disease,[350] retinopathy,[351] amputations, hospitalization for cardiovascular outcomes,[352] and diabetes-related mortality.[353] Finally, racial and ethnic minorities are less likely to have controlled diabetes (HbA1c <7 percent), but are more likely to be on oral treatment only for diabetes.[354]

Applicability

The applicability of these studies depends largely on the similarity of the study populations to the U.S. population with type 2 diabetes and the similarity of the interventions to usual clinical care (e.g., comparability of the drug interventions including dosing and duration of exposure to drugs). The included studies generally had populations, interventions, outcomes, and settings applicable to U.S. adults with type 2 diabetes, with a few notable exceptions, as described below.

Study population differences are the most pronounced threat to applicability. Study participants were mainly middle-aged (mean age in the mid 50s), overweight or obese adults who had diabetes for 3 to 7 years at the start of the studies. This is similar to the U.S. population with type 2 diabetes, which has a mean age of 60.5 years and a mean body mass index of 33 kg/m2 (23.5 percent overweight, 65.3 percent obese).[355] However, most studies excluded people older than 75 or 80 years of age and excluded people with significant renal, hepatic, and cardiovascular disease, and other significant co-morbid conditions, making these studies less applicable, given that 52 percent of US adults with diabetes are older than 60 years of age, and just over 25 percent have a history of cardiovascular disease.[355] When race was reported in the included studies, most subjects were Caucasian, although about 10 to 20 percent of study participants were of other races. These studies are, therefore, less applicable to people of different races and ethnicities, who make up about 40 percent of the US population with diabetes and, importantly, these groups have a greater diabetes burden than Caucasians (i.e., African Americans, Hispanics, Asian Americans, and American Indians).[1, 355]

Characteristics of the interventions also impact applicability, and most studies used dosing, frequency, and monitoring comparable to usual care. However, a threat to applicability relates to the duration of drug exposure, especially for glycemic control. The vast majority of RCTs lasted for 2 years or less. In usual care, patients with diabetes are on medications for over 10 years and are on multiple medications that impact adherence and side effects. Also, the glycemic response to medications may degrade over time; retained insulin sensitivity may allow insulin sensitizers (like metformin) to work longer as monotherapy than medications that are not insulin sensitizers. Also, in roughly one-third of the included trials, rescue therapy was used if participants did not meet specific glycemic goals, and participants were often censored from the study at that time. Thus, the results of these studies may not reflect what will occur with the clinical usage of the studied medications.

We generally had few concerns regarding applicability of the trial settings to usual care. While many trials did not take place exclusively in the United States, they did occur in similar settings. About half the trials occurred partly or exclusively in the United States, Italy, and/or were multinational; the rest of the trials occurred in developed or newly industrialized countries.

However, few trials (about 25 percent) reported on the setting of recruitment, such as primary care or specialty care, so we cannot definitively comment on how like this is to usual care.

Implications for Clinical and Policy Decisionmaking

This update provides additional evidence supporting metformin as the first-line medication therapy to treat type 2 diabetes, when tolerated; the evidence also supports the addition to metformin of a number of treatment options, based on patient preferences. Not only is metformin favored on the intermediate outcomes of HbA1c and weight, and not associated with serious adverse events, we found more conclusive evidence to support that cardiovascular mortality is lower with metformin compared with sulfonylureas. This evidence supports current guidelines, such as the American College of Physicians[356] and American Diabetes Association[26] guidelines, which recommend metformin as a first-line treatment choice. The American Association of Clinical Endocrinologists[19] guideline also lists metformin as one of its first-line choices for treatment of type 2 diabetes, although it allows more flexibility in the choice of first-line therapy.

Metformin is currently contraindicated in patients with "renal disease or renal dysfunction,"[357] because of concerns for an increased risk of lactic acidosis in this population. However, as described above, this risk is small and may not be higher than the background risk of lactic acidosis for patients with type 2 diabetes.[332, 333] Twenty-two percent of patients with type 2 diabetes in the United States are estimated to have at least mild chronic kidney disease, indicating a large group of patients with type 2 diabetes who are not currently candidates for metformin therapy.[358] Furthermore, some patients with type 2 diabetes are unable tolerate the side effects of metformin. The selection of initial diabetes therapy is an important clinical question for this relatively large population in which metformin is contraindicated or not tolerated. We evaluated non-metformin-based monotherapy comparisons in this report and demonstrated that, with the exception of DPP-4 inhibitors, which are not as effective in reducing HbA1c as metformin, the other monotherapies generally decrease HbA1c similarly (and comparably) to metformin. As described in detail, the other monotherapies' effects on weight vary as do their adverse effects, such as congestive heart failure (increased risk for thiazolidinediones), hypoglycemia (highest risk with sulfonylureas, including for severe hypoglycemia for many comparisons), gastrointestinal side effects (nausea and vomiting with GLP-1 receptor agonists), and genital mycotic infections (increased risk for SGLT-2 inhibitors). Most importantly, we do not have conclusive evidence on the relative long-term effects of non-metformin-based monotherapy on all-cause mortality or cardiovascular outcomes and rare, serious adverse events (e.g., pancreatitis risk with GLP-1 receptor agonists). Therefore, the alternative to metformin initial therapy is unclear and, seemingly, must be based on individual patient factors (e.g., HbA1c goal, risk of hypoglycemia) and preferences (e.g., avoidance of weight gain, cost).

Similarly, our evaluation of metformin-based combination therapies provides some insight into the selection of add-on therapy to metformin but is not definitive, because of the uncertainty of long-term outcomes and differential effects on weight and side effects. Comparisons of the metformin-based combinations suggested similar HbA1c-lowering for the metformin-based combination therapies (except for DPP-4 inhibitors added to metformin having a smaller HbA1c-lowering effect), differential weight effects, highest hypoglycemia risk with metformin plus a sulfonylurea, highest risk of gastrointestinal side effects with metformin plus GLP-1 receptor agonists, and increased risk of genital mycotic infections with metformin plus an SGLT-2 inhibitor.

As the newer medications (DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists) remain on the market, become available as generics, and have additional data on comparative efficacy (for long-term outcomes) and safety, these newer medications may be preferred by patients. Therefore, the continued emphasis in guidelines about accounting for patient preferences when choosing therapy will be critical.[26] In terms of cost, pioglitazone is the newest agent that has a generic. The first patent for Byetta expires in December 2016 and Januvia will have a patent expiry in 2017. If generics are available soon after, this will give patients and clinicians more affordable options for therapy.

In summary, we did not find large differences in HbA1c-lowering effects of the diabetes medications studied, except for DPP-4 inhibitors, which are not as effective as metformin. Weight effects of the medications are differential, and there is only evidence on cardiovascular mortality to support metformin over sulfonylureas as monotherapy. Each class of drug has different side effects (e.g., hypoglycemia, GI side effects, congestive heart failure), and the evidence on rare, serious side effects is less strong. Therefore, factors such as patient preferences and costs are likely to continue to drive selection of and adherence to the diabetes medications.

Limitations of the Comparative Effectiveness Review Process

Several important limitations to our updated systematic review deserve mention. Although this was an update of a comprehensive review published in 2007 and an update in 2011, we focused this update *a priori* on studies with active control comparators, which are most relevant for clinical practice. Placebo-controlled trials had been included in the original 2007 review but excluded in the 2011 update. In general, the majority of placebo-controlled trials are short. However, the exclusion of placebo-controlled trials has implications for the review, including the inability to evaluate rare outcomes using indirect comparisons. To conclude from an active-control study that one medication is more effective than another requires prior knowledge that the active-control drug has been studied previously and is known to be more effective than placebo. Because the 2007 review had included placebo-controlled trials, we know that many drugs were more effective than placebo for the intermediate outcomes for many drug comparisons. However, this assumption may be less valid for the newer medications, where evidence on comparisons with placebo from other systematic reviews, such as the Cochrane Reviews,[277, 283] will also be helpful in making conclusions.

In addition, our inclusion criteria required that all studies fit into one or more of the pre-specified comparisons of interest (Table 2), which identified specific drug-drug or two-drug comparisons. For example, studies that included any number of "background medications" were excluded. Our rationale was to avoid attributing outcomes to the medication of interest when it was truly due to the background medication. This was especially important because of our goal of evaluating two-drug combinations. Applying the inclusion criteria, which required pre-specified comparisons of interest, had several implications. This criteria required the exclusion of several large trials,[9-12, 312, 359-363] some of which evaluated HbA1c-lowering strategies rather than individual medications, as well as some smaller trials and observational studies.

Of note, the RECORD study[49] was included for the intermediate outcomes but excluded for the long-term and safety outcomes, because it did not stratify these outcomes by comparisons of interest. While excluding this study for these outcomes lowered our evidence grade for congestive heart failure, it did not change the overall conclusion. Another consequence of requiring direct comparisons of interest was that some of the recent studies of exenatide[174, 364-366]

and liraglutide[261, 367-369] as add-on therapy to metformin did not have a specific comparison of interest and were therefore excluded. However, these studies would not have changed our findings as HbA1c were similar to those observed in the included studies, and these studies did not report on mortality, cardiovascular outcomes, pancreatitis, or cancer – outcomes of particular interest for these agents.

We also had strict criteria for including only medium- to high-quality observational studies. For instance, we required observational studies to have accounted for confounding by age, gender, race/socioeconomic status, and co-morbid conditions. The article could have used propensity score methodologies or other appropriate methods to account for differences between groups, or could have restricted to one race or socioeconomic status, for examples. By excluding observational studies with a higher risk of bias, we included only observational studies that could provide the most valid results. This resulted in the exclusion of many observational studies of harms, which could have strengthened the evidence base, but this was necessary to reduce confounding by indication in these studies.

We selected Key Questions focused on intermediate and long-term clinical outcomes through a topic refinement at the beginning of this process, which involved input from stakeholders on the Technical Expert Panel. Diabetes care is an extensive field, and we note the omission of key outcomes. For example, we did not collect information about patient-reported outcomes, such as medication adherence and barriers to adherence, health-related quality of life, or treatment satisfaction. These outcomes are important, because they may mediate the efficacy of treatment, and also are valuable to patients and clinicians. Future reviews with methodologies designed to capture many different study designs, including qualitative studies, and use of a wide range of measures, are needed to address these outcomes. For microvascular outcomes, we included studies evaluating proximal measures such as change in retinal exam or changes in microalbuminuria which may be less clinically relevant than other microvascular outcomes of blindness and changes in estimated glomerular filtration rate. However, we were unable to conclude anything about the comparative effects on the microvascular outcomes due to lack of sufficient evidence. These distinctions may become more important as more evidence accrues on these different microvascular outcomes. Although we assessed the mean difference in HbA1c between intervention groups in Key Question 1, we did not include the durability of HbA1c changes over time as an outcome, which may best be addressed using long-term well-designed observational studies.

In terms of pooling results, we chose to combine similar studies for pooled estimates. For study duration, we chose to combine similar duration studies which were often less than or equal to 52 weeks. While between-group differences might vary between 12, 24 and 52 week studies, we did not find substantial clinical or statistical heterogeneity related to these study duration differences in our pooled analyses. We also chose to combine results by drug class for most comparisons, except where clinically indicated (e.g., separated rosiglitazone and pioglitazone in cardiovascular comparisons). This may have led us to miss small differences within a drug class. However, if there was clinical or statistical heterogeneity noted among the studies, we evaluated for differences by drug type. For instance, we did not combine GLP-1 receptor agonists together in the hemoglobin A1c section (unless all studies used a single drug within the class, such as exenatide) owing to potential differences by drug type in glycemic control. This potential clinical heterogeneity was noted prior to combining the individual medications and was also identified when examining statistical heterogeneity among those studies. Also, in the 2007 report,[15] we found that glyburide/glibenclamide had a higher absolute risk difference of mild, moderate, or

total hypoglycemia compared with other sulfonylureas (pooled RD 3%; 95% CI, 0.5% to 5%). In this update, which focused on interclass comparisons, the studies that included glyburide/glibenclamide as the sulfonylurea did not consistently have larger between-group differences in hypoglycemia risk compared to the other sulfonylurea studies. Therefore, these studies were combined with the other sulfonylurea comparisons for hypoglycemia.

Limitations of the Evidence Base

The major limitation of the evidence base was a lack of evidence supporting conclusions on the comparative *long-term* (followup at least 2 years) clinical (mortality, cardiovascular outcomes, and microvascular outcomes) and safety outcomes of the medications of interest. Given the low event rates for these outcomes and the timeframe in which they develop, RCTs, while extremely helpful, do not feasibly provide all of the evidence on long-term outcomes. Once we applied selection criteria to account for confounding by key factors, including confounding by indication, an important threat to validity in this setting, we did not identify many observational studies on the long-term and rare outcomes. Given the resources needed, not surprisingly, we did not identify any RCTs designed to evaluate long-term outcomes as the primary outcome. The included RCT evidence was underpowered for these outcomes based on the combination of small sample sizes, low event rates, and short study durations (generally 12 months or less). Substantial losses to followup, often differential across study arms, were another major limitation to the evidence on long-term clinical and safety outcomes. Additional limitations of the evidence base on long-term and safety outcomes included lack of reporting on these outcomes (including lack of reporting across all study arms), lack of active ascertainment of safety outcomes, and lack of an intention-to-treat approach.

As expected, the vast majority of included RCTs were industry-sponsored, raising the possibility of publication bias and other forms of bias, such as selective reporting of outcomes. While publication bias and reporting bias generally were not found, publication bias analyses have limited power, owing to the small numbers of studies for any given comparison. Although we cannot conclude that bias was present, we have to be especially concerned about the following issues identified across the included RCTs (*which are important regardless of sponsorship*):

- For the long-term clinical and safety outcomes, many studies reported an event in one arm but not in the comparator arm, making it challenging to compare medications.
- Several studies failed to report the significance of between-group differences and the measures of dispersion, thereby hindering efforts to estimate effect size across trials for intermediate outcomes.
- Some trials compared medications using dissimilar doses, limiting our ability to draw conclusions about efficacy.

Also, many studies had high rates of withdrawals; even if the studies described the rates of withdrawals, they often did not use a valid method for accounting for missing data.[370] Finally, authors of the included randomized trials often did not describe their method of randomization and often did not describe double-blinding, making it difficult to appropriately assess risk of bias of individual studies.

Research Gaps and Future Research Needs

Based on the limitations of the evidence base, using the PICOT framework, we highlight several major gaps in the evidence in Table 127. We report these for all of the Key Questions (Key Questions 1-4; comparative effectiveness and safety) together, to avoid duplicating research gaps that apply to more than one Key Question. We also added a specific "methodologic" category to complement the content-oriented research gaps. We provide recommendations on future research needs corresponding to these research gaps (Table 127).

In particular, we want to highlight the importance of future research using high-quality observational studies to determine the comparative effects of diabetes medications on long-term clinical and safety outcomes. Multi-year (or decade) trials are often infeasible. Supplementing the rare RCT that can be conducted for these outcomes with truly high-quality observational studies is paramount.

We propose that, at a minimum, such observational studies will need to follow patients over time, analyze similar comparison groups, and account for confounding by indication (including duration of diabetes and co-morbid conditions). Databases with sufficient sample size, followup over time, data on treatments (including doses and duration), and confounders, such as demographics, duration of diabetes, and co-morbid conditions, will be necessary. A recent review by Patorno et al. provided a thorough evaluation of threats to the validity of observational studies of diabetes medications and cardiovascular outcomes and outlined approaches to avoiding these biases.[371] Briefly, the following are major methodological pitfalls and strategies to avoiding biases in the conduct of future observational studies of the comparative effectiveness and safety of diabetes medications[371]:

- **Confounding by indication**: Basic variables which must be considered to reduce confounding by indication include demographics, duration of diabetes, and co-morbid conditions. Many statistical methods may be sufficient (e.g., multivariate regression, restriction, instrumental variables), but propensity score methods may be the strongest to handle confounding by indication. In particular, high-dimensional propensity score algorithms may be the most rigorous, as they can help deal with unmeasured confounders.
- **Immortal time bias**: Prospective studies that define cohort entry based on exposure to a drug (versus calendar time or diagnosis of diabetes during a specified window), that have covariate information prior to exposure, and that do not condition cohort entry on events that occur during followup (e.g., initiation of insulin) are most likely to avoid immortal time bias.
- **Time- and cumulative exposure-varying incidence of outcomes:** The effects of medications on the outcomes of interest may vary over time and with cumulative drug exposure; study designs evaluating new users of drugs and accounting for exposure time will minimize biases due to time- and cumulative exposure-dependent effects of medications.
- **Reverse causation:** Analyses allowing for lag time after exposure can reduce the chance of reverse causality.
- **Informative censoring**: Censoring of observations when a drug exposure stops may lead to informative censoring, because reasons related to drug continuation may also be related to the outcome of interest. Analyses accounting for latency of drug effects can address this issue.

- **Time-varying drug exposure:** Although time-to-event analyses are often preferred to evaluate risk factors for outcomes such as cardiovascular disease, in the case of diabetes, drug changes may be related to the outcome. Sensitivity analyses can be used to support analyses based on time-to-event analyses.
- **Time-dependent confounders:** Inclusion of important confounding factors, such as co-morbid conditions that change over time, and the use of statistical methods, such as marginal structural models, may be helpful in handling such confounders.

Table 127. Evidence gaps and future research needs for the comparative effectiveness and safety of diabetes medications for adults with type 2 diabetes

PICOT Category	Evidence Gap	Future Research Needs
Population		
	• Lack of study of older adults, racial/ethnic minorities, and persons with co-morbid conditions such as significant renal, cardiovascular and hepatic impairment. • Limited evidence on *a priori* subgroups of interest such as older adults, racial/ethnic minorities, sex, and BMI	• Studies which include diverse populations • Studies with an *a priori* plan to investigate differences by important subgroups of interest
Interventions & Comparators		
HbA1c, weight, hypoglycemia and GI adverse events	• Limited information on GLP-1 receptor agonist comparisons as monotherapy and in combination with metformin versus specific diabetes medication comparators. • Limited information on metformin plus insulin versus other metformin-based combinations.	• RCTs evaluating the GLP-1 receptor agonists as monotherapy and in combination with metformin. If adding GLP-1 receptor agonists to different background medications, then RCTs should conduct stratified randomization by background medication and evaluate effects by background medication. • RCTs evaluating intermediate outcomes for metformin plus the addition of insulin with other metformin-based combinations, and in particular metformin plus a GLP-1 receptor agonist would be useful for patients and clinicians contemplating an add-on injectable to metformin.
Outcomes		
All-cause mortality and macrovascular and microvascular outcomes	• Limited information on macrovascular outcomes and death • Existing evidence underpowered • Limited number of high-quality observational studies • No conclusive evidence on microvascular outcomes • No RCTs evaluated these outcomes as a primary outcome • Inconsistent outcome definitions, ascertainment, and reporting in each study arm	• High-quality observational studies for all comparisons • Longer duration RCTs for all comparisons evaluating macrovascular and microvascular events as primary outcomes • Standardized definitions for macrovascular and especially microvascular outcomes (e.g., incident nephropathy based on eGFR and urine albumin:creatinine ratios) • Reporting on outcomes in all arms of RCTs

Table 127. Evidence gaps and future research needs for the comparative effectiveness and safety of diabetes medications for adults with type 2 diabetes (continued)

PICOT Category	Evidence Gap	Future Research Needs
Rare safety outcomes	• Existing evidence underpowered • Lack of high-quality observational studies • Inconsistent outcome definitions, ascertainment, and reporting in each study arm, especially for pancreatitis and cancer • No conclusive evidence on any of the following adverse events: CHF, pancreatitis, cancer, liver injury, lactic acidosis, severe allergic reactions, macular edema • No conclusive evidence on volume depletion for SGLT-2 inhibitor comparisons	• High-quality observational studies for rare outcomes* • Specific safety outcomes and drugs require further study including the following: o CHF – DPP-4 inhibitors o Macular edema – TZDs o Pancreatitis – DPP-4 inhibitors and GLP-1 receptor agonists o Thyroid cancer – GLP-1 receptor agonists o Volume depletion – SGLT-2 inhibitors o Ketoacidosis – SGLT-2 inhibitors • RCTs o Active ascertainment of all safety outcomes o Standardized definitions for all safety outcomes o Reporting on safety outcomes in all arms
Timing	• Most evidence is for short-term outcomes as few studies lasted more than 2 years	• Longer duration studies (>2 years) o To determine durability of short-term comparative effects on HbA1c and weight o To determine long-term clinical effectiveness (e.g., all-cause mortality and cardiovascular outcomes) and safety
Methodological	• High, and often differential, losses to followup in RCTs • Lack of reporting on randomization methods (for RCTs) • Lack of reporting on allocation concealment, blinding, and withdrawals for all studies • Lack of appropriate accounting for confounding in observational studies • Lack of reporting on treatments in observational studies	• Complete or near-complete followup in RCTs (focus on retention) • Appropriate methods to account for losses to followup if needed (e.g., multiple imputation) • Reporting on methods for randomization, allocation concealment, and blinding in RCTs • High-quality observational studies for long-term comparative effectiveness and safety of diabetes medications*

BMI = body mass index; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; RCT = randomized controlled trial; SGLT-2 sodium-glucose co-transporter-2; TZD = thiazolidinediones
*See text above for more detail.

Conclusions

Although the comparative long-term benefits and harms of most diabetes medications remain unclear, the evidence supports use of metformin as a first-line agent, because of its beneficial effects on HbA1c, weight, and long-term outcomes (cardiovascular mortality benefit for metformin versus sulfonylureas, in particular), and its relative safety. With the exception of DPP-4 inhibitors, which have smaller effects on HbA1c reduction compared to metformin, the HbA1c-lowering of the other diabetes medications are similar, for monotherapy and metformin-based combination comparisons. The alternative to metformin monotherapy is unclear because of a lack of evidence on long-term effectiveness and safety outcomes on the other monotherapy comparisons. Likewise, the comparative effectiveness of metformin-based combinations for long-term macrovascular, microvascular, and rare safety outcomes is unclear. Monotherapy and metformin-based combination comparisons have differential effects on weight and side effects (e.g., hypoglycemia, GI side effects). In this report, we provide comprehensive information on the relative benefits and harms of diabetes medications to inform personalized treatment choices by patients and their clinicians, as well as to support decisionmaking by payers and regulators.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014; http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf. Accessed 2015 February 26.
2. Lee JW, Brancati FL, Yeh HC. Trends in the prevalence of type 2 diabetes in Asians versus whites: results from the United States National Health Interview Survey, 1997-2008. Diabetes Care. 2011 Feb;34(2):353-7. PMID: 21216863.
3. Nichols GA, Schroeder EB, Karter AJ, et al. Trends in diabetes incidence among 7 million insured adults, 2006-2011: the SUPREME-DM project. Am J Epidemiol. 2015 Jan 1;181(1):32-9. PMID: 25515167.
4. Maruthur NM. The growing prevalence of type 2 diabetes: increased incidence or improved survival? Curr Diab Rep. 2013 Dec;13(6):786-94. PMID: 24072478.
5. Centers for Disease Control and Prevention. Diabetes Public Health Resource: Incidence ang Age at Diagnosis. 2013; http://www.cdc.gov/diabetes/statistics/incidence_national.htm. Accessed 2015 January 27.
6. Anon. Economic costs of diabetes in the U.S. In 2007. Diabetes Care. 2008 Mar;31(3):596-615. PMID: 18308683.
7. Anon. Standards of medical care in diabetes-2014. Diabetes Care. 2014;37(SUPPL.1):S14-S80. PMID: 24357209.
8. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Spectrum. 2012;25(3):154-71. PMID: 22517736
9. Anon. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65. PMID: 9742977.
10. Anon. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53. PMID: 9742976.
11. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. The New England journal of medicine. 2009 Jan 8;360(2):129-39. PMID: 19092145.
12. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. The New England journal of medicine. 2008 Jun 12;358(24):2545-59. PMID: 18539917.
13. Papademetriou V, Lovato L, Doumas M, et al. Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. Kidney Int. 2014 Sep 17. PMID: 25229335.
14. Saremi A, Schwenke DC, Bahn G, et al. The effect of intensive glucose lowering therapy among major racial/ethnic groups in the Veterans Affairs Diabetes Trial. Metabolism. 2015 Feb;64(2):218-25. PMID: 25456099.
15. Bolen S, Wilson L, Vassy J, et al. Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes. Comparative Effectiveness Review No 8 (Prepared by the Johns Hopkins Evidence-based Practice Center under Contract No 290-02-0018). Rockville, MD: Agency for Healthcare Research and Quality; 2007.

16. Bennett WL, Wilson LM, Bolen S, et al. Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 27. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.) AHRQ Publication No. 11-EHC038-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2011.

17. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med. 2007 Sep 18;147(6):386-99. PMID: 17638715.

18. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011 May 3;154(9):602-13. PMID: 21403054.

19. Garber A, Abrahamson M, Barzilay J, et al. American association of clinical endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. Endocrine Practice. 2013;19(SUPPL. 2):1-48. PMID: 23816937.

20. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a position statement of the american diabetes association and the european association for the study of diabetes. Diabetes Care. 2015;38(1):140-9. PMID: 25538310

21. Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update). London: Royal College of Physicians of London.; 2008.

22. Colhoun HM, Livingstone SJ, Looker HC, et al. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012 Nov;55(11):2929-37. PMID: 22945303.

23. Lu CJ, Sun Y, Muo CH, et al. Risk of stroke with thiazolidinediones: a ten-year nationwide population-based cohort study. Cerebrovasc Dis. 2013;36(2):145-51. PMID: 24029780.

24. Mahaffey KW, Hafley G, Dickerson S, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J. 2013 Aug;166(2):240-9 e1. PMID: 23895806.

25. Mamtani R, Haynes K, Bilker WB, et al. Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. J Natl Cancer Inst. 2012 Sep 19;104(18):1411-21. PMID: 22878886.

26. Anon. (7) Approaches to glycemic treatment. Diabetes Care. 2015 Jan;38 Suppl:S41-8. PMID: 25537707.

27. Turner LW, Nartey D, Stafford RS, et al. Ambulatory treatment of type 2 diabetes in the U.S., 1997-2012. Diabetes Care. 2014 Apr;37(4):985-92. PMID: 24198301.

28. Raebel MA, Xu S, Goodrich GK, et al. Initial antihyperglycemic drug therapy among 241 327 adults with newly identified diabetes from 2005 through 2010: a surveillance, prevention, and management of diabetes mellitus (SUPREME-DM) study. Ann Pharmacother. 2013 Oct;47(10):1280-91. PMID: 24259692.

29. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-S45. PMID: 24222016.

30. Anon. (8) Cardiovascular disease and risk management. Diabetes Care. 2015 Jan;38 Suppl:S49-57. PMID: 25537708.

31. Tsertsvadze A, Maglione M, Chou R, et al. Updating comparative effectiveness reviews: current efforts in AHRQ's Effective Health Care Program. J Clin Epidemiol. 2011 Nov;64(11):1208-15. PMID: 21684114.

32. Higgins JPT, S. G. Cochrane handbook for systemic reviews of interventions Version 5.1.0. 2011; http://handbook.cochrane.org/. Accessed Oxford, England.

33. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;17(1):1-12. PMID: 8721797.

34. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998 Jun;52(6):377-84. PMID: 9764259.

35. Institute of Medicine. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press; 2011; books.nap.edu/openbook.php?record_id=13059&page=81. Accessed 2014 July 9.

36. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. The New England journal of medicine. 2008 Feb 7;358(6):580-91. PMID: 18256393.

37. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60. PMID: 12958120.

38. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID: 3802833.

39. Cornell JE, Mulrow CD, Localio R, et al. Random-Effects Meta-analysis of Inconsistent Effects: A Time for Change. Ann Intern Med. 2014 Feb 18;160(4):267-70. PMID: 24727843.

40. Balshem H, Stevens A, Ansari M, et al. Finding Grey Literature Evidence and Assessing for Outcome and Analysis Reporting Biases When Comparing Medical Interventions: AHRQ and the Effective Health Care Program Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville MD2008.

41. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994 Dec;50(4):1088-101. PMID: 7786990.

42. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629-34. PMID: 9310563.

43. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.

44. Singh N. Diabetes, heart rate, and mortality. J Cardiovasc Pharmacol Ther. 2002 Apr;7(2):117-29. PMID: 12075400.

45. Lenters-Westra E, Schindhelm RK, Bilo HJ, et al. Differences in interpretation of haemoglobin A1c values among diabetes care professionals. Neth J Med. 2014 Nov;72(9):462-6. PMID: 25431391.

46. Dupont WD, Plummer WD, Jr. Power and sample size calculations. A review and computer program. Control Clin Trials. 1990 Apr;11(2):116-28. PMID: 2161310.

47. Tosi F, Muggeo M, Brun E, et al. Combination treatment with metformin and glibenclamide versus single-drug therapies in type 2 diabetes mellitus: a randomized, double-blind, comparative study. Metabolism. 2003 2003 Jul;52(7):862-7. PMID: 12870162

48. Alba M, Ahren B, Inzucchi SE, et al. Sitagliptin and pioglitazone provide complementary effects on postprandial glucose and pancreatic islet cell function. Diabetes Obes Metab. 2013 Dec;15(12):1101-10. PMID: 23782502.

49. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 Jun 5;373(9681):2125-35. PMID: 19501900.

50. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. The New England journal of medicine. 2006 Dec 7;355(23):2427-43. PMID: 17145742.

51. Bergenstal RM, Forti A, Chiasson JL, et al. Efficacy and safety of taspoglutide versus sitagliptin for type 2 diabetes mellitus (T-emerge 4 trial). Diabetes Ther. 2012 Dec;3(1):13. PMID: 23138449.

52. Tolman KG, Freston JW, Kupfer S, Perez A. Liver safety in patients with type 2 diabetes treated with pioglitazone: results from a 3-year, randomized, comparator-controlled study in the US. Drug Saf. 2009;32(9):787-800. PMID: 19670918.

53. Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. Lancet. 2012 Jun 16;379(9833):2270-8. PMID: 22683137.

54. Del Prato S, Nauck M, Duran-Garcia S, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in type 2 diabetes patients: 4-year data. Diabetes Obes Metab. 2015 Mar 4. PMID: 25735400.

55. Derosa G, Maffioli P, Salvadeo SA, et al. Direct comparison among oral hypoglycemic agents and their association with insulin resistance evaluated by euglycemic hyperinsulinemic clamp: the 60's study. Metabolism. 2009 2009 Apr 22. PMID: 19394976

56. Gupta AK, Smith SR, Greenway FL, Bray GA. Pioglitazone treatment in type 2 diabetes mellitus when combined with portion control diet modifies the metabolic syndrome. Diabetes Obes Metab. 2009 2009 Apr;11(4):330-7. PMID: 19267711

57. Erdem G, Dogru T, Tasci I, et al. The effects of pioglitazone and metformin on plasma visfatin levels in patients with treatment naive type 2 diabetes mellitus. Diabetes Res Clin Pract. 2008 2008 Nov;82(2):214-8. PMID: 18778865

58. Iliadis F, Kadoglou NP, Hatzitolios A, et al. Metabolic effects of rosiglitazone and metformin in Greek patients with recently diagnosed type 2 diabetes. In Vivo. 2007 2007 Nov-Dec;21(6):1107-14. PMID: 18210765

59. Rosenstock J, Rood J, Cobitz A, et al. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab. 2006 2006 Nov;8(6):650-60. PMID: 17026489

60. Yamanouchi T, Sakai T, Igarashi K, et al. Comparison of metabolic effects of pioglitazone, metformin, and glimepiride over 1 year in Japanese patients with newly diagnosed Type 2 diabetes. Diabet Med. 2005 2005 Aug;22(8):980-5. PMID: 16026361

61. Ramachandran A, Snehalatha C, Salini J, Vijay V. Use of glimepiride and insulin sensitizers in the treatment of type 2 diabetes--a study in Indians. J Assoc Physicians India. 2004 2004 Jun;52:459-63. PMID: 15645955

62. Schernthaner G, Matthews DR, Charbonnel B, et al. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. J Clin Endocrinol Metab. 2004 2004 Dec;89(12):6068-76. PMID: 15579760

63. Lawrence JM, Reid J, Taylor GJ, et al. Favorable effects of pioglitazone and metformin compared with gliclazide on lipoprotein subfractions in overweight patients with early type 2 diabetes. Diabetes Care. 2004 2004 Jan;27(1):41-6. PMID: 14693964

64. Pavo I, Jermendy G, Varkonyi TT, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. J Clin Endocrinol Metab. 2003 2003 Apr;88(4):1637-45. PMID: 12679450

65. Hallsten K, Virtanen KA, Lonnqvist F, et al. Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes. Diabetes. 2002 2002 Dec;51(12):3479-85. PMID: 12453903

66. Kiyici S, Ersoy C, Kaderli A, et al. Effect of rosiglitazone, metformin and medical nutrition treatment on arterial stiffness, serum MMP-9 and MCP-1 levels in drug naive type 2 diabetic patients. Diabetes Research and Clinical Practice. [doi: DOI: 10.1016/j.diabres.2009.07.004]. 2009 2009/10//;86(1):44-50. PMID: 19674806

67. Perez A, Zhao Z, Jacks R, Spanheimer R. Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM. Curr Med Res Opin. 2009 Dec;25(12):2915-23. PMID: 19827910.

68. Kato T, Sawai Y, Kanayama H, et al. Comparative study of low-dose pioglitazone or metformin treatment in Japanese diabetic patients with metabolic syndrome. Exp Clin Endocrinol Diabetes. 2009 Nov;117(10):593-9. PMID: 19924605.

69. Esteghamati A, Ghasemiesfe M, Mousavizadeh M, et al. Pioglitazone and metformin are equally effective in reduction of chemerin in patients with type 2 diabetes. J Diabetes Investig. 2014 May 4;5(3):327-32. PMID: 24843782.

70. Erem C, Ozbas HM, Nuhoglu I, et al. Comparison of effects of gliclazide, metformin and pioglitazone monotherapies on glycemic control and cardiovascular risk factors in patients with newly diagnosed uncontrolled type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2014 May;122(5):295-302. PMID: 24710641.

71. Genovese S, De Berardis G, Nicolucci A, et al. Effect of pioglitazone versus metformin on cardiovascular risk markers in type 2 diabetes. Adv Ther. 2013 Feb;30(2):190-202. PMID: 23359066.

72. Taslimi S, Esteghamati A, Rashidi A, et al. Treatment with pioglitazone is associated with decreased preprandial ghrelin levels: a randomized clinical trial. Peptides. 2013 Feb;40:89-92. PMID: 23276779.

73. Russell-Jones D, Cuddihy RM, Hanefeld M, et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. Diabetes Care. 2012 Feb;35(2):252-8. PMID: 22210563.

74. Yoon KH, Shin JA, Kwon HS, et al. Comparison of the efficacy of glimepiride, metformin, and rosiglitazone monotherapy in korean drug-naive type 2 diabetic patients: the practical evidence of antidiabetic monotherapy study. Diabetes Metab J. 2011 Feb;35(1):26-33. PMID: 21537410.

75. Fidan E, Onder Ersoz H, Yilmaz M, et al. The effects of rosiglitazone and metformin on inflammation and endothelial dysfunction in patients with type 2 diabetes mellitus. Acta Diabetol. 2011 Dec;48(4):297-302. PMID: 21424914.

76. Esposito K, Maiorino MI, Di Palo C, et al. Effects of pioglitazone versus metformin on circulating endothelial microparticles and progenitor cells in patients with newly diagnosed type 2 diabetes--a randomized controlled trial. Diabetes Obes Metab. 2011 May;13(5):439-45. PMID: 21255215.

77. Esteghamati A, Azizi R, Ebadi M, et al. The Comparative Effect of Pioglitazone and Metformin on Serum Osteoprotegerin, Adiponectin and Intercellular Adhesion Molecule Concentrations in Patients with Newly Diagnosed Type 2 Diabetes: a Randomized Clinical Trial. Exp Clin Endocrinol Diabetes. 2015 Jan 21. PMID: 25607338.

78. Turkmen Kemal Y, Guvener Demirag N, Yildirir A, et al. Effects of rosiglitazone on plasma brain natriuretic peptide levels and myocardial performance index in patients with type 2 diabetes mellitus. Acta Diabetol. 2007 2007 Sep;44(3):149-56. PMID: 17721754

79. Gupta RK, Rehan HS, Rohatagi A, et al. The effect of glipizide, metformin and rosiglitazone on nontraditional cardiovascular risk factors in newly diagnosed patients with type 2 diabetes mellitus. International journal of diabetes in developing countries [serial on the Internet]. 2010; (3): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/971/CN-00797971/frame.html.

80. Goldstein BJ, Feinglos MN, Lunceford JK, et al. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care. 2007 2007 Aug;30(8):1979-87. PMID: 17485570

81. Williams-Herman D, Johnson J, Teng R, et al. Efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: a 54-week study. Curr Med Res Opin. 2009 2009 Mar;25(3):569-83. PMID: 19232032

82. Aschner P, Katzeff HL, Guo H, et al. Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. Diabetes Obes Metab. 2010 Mar;12(3):252-61. PMID: 20070351.

83. Jadzinsky M, Pfutzner A, Paz-Pacheco E, et al. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes Obes Metab. 2009 2009 Jun;11(6):611-22. PMID: 19515181

84. Pratley RE, Fleck P, Wilson C. Efficacy and safety of initial combination therapy with alogliptin plus metformin versus either as monotherapy in drug-naive patients with type 2 diabetes: a randomized, double-blind, 6-month study. Diabetes Obes Metab. 2014 Jul;16(7):613-21. PMID: 24400655.

85. Williams-Herman D, Johnson J, Teng R, et al. Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. Diabetes Obes Metab. 2010 May;12(5):442-51. PMID: 20415693.

86. Haak T, Meinicke T, Jones R, et al. Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2012 Jun;14(6):565-74. PMID: 22356132.

87. Pfutzner A, Paz-Pacheco E, Allen E, et al. Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks. Diabetes Obes Metab. 2011 Jun;13(6):567-76. PMID: 21342412.

88. Henry RR, Murray AV, Marmolejo MH, et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract. 2012 May;66(5):446-56. PMID: 22413962.

89. List JF, Woo V, Morales E, et al. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care. 2009 Apr;32(4):650-7. PMID: 19114612.

90. Ferrannini E, Berk A, Hantel S, et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: An active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care. 2013;36(12):4015-21. PMID: 24186878

91. Umpierrez G, Povedano ST, Manghi FP, et al. Efficacy and Safety of Dulaglutide Monotherapy Versus Metformin in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-3). Diabetes Care. 2014 May 19. PMID: 24842985.

92. Yuan GH, Song WL, Huang YY, et al. Efficacy and tolerability of exenatide monotherapy in obese patients with newly diagnosed type 2 diabetes: a randomized, 26 weeks metformin-controlled, parallel-group study. Chin Med J (Engl). 2012 Aug;125(15):2677-81. PMID: 22931974.

93. Teramoto T, Yamada N, Shirai K, Saito Y. Effects of pioglitazone hydrochloride on Japanese patients with type 2 diabetes mellitus. J Atheroscler Thromb. 2007 2007 Apr;14(2):86-93. PMID: 17485893

94. Hanefeld M, Patwardhan R, Jones NP. A one-year study comparing the efficacy and safety of rosiglitazone and glibenclamide in the treatment of type 2 diabetes. Nutr Metab Cardiovasc Dis. 2007 2007 Jan;17(1):13-23. PMID: 17174222

95. Jain R, Osei K, Kupfer S, et al. Long-term safety of pioglitazone versus glyburide in patients with recently diagnosed type 2 diabetes mellitus. Pharmacotherapy. 2006 2006 Oct;26(10):1388-95. PMID: 16999648

96. Nakamura T, Matsuda T, Kawagoe Y, et al. Effect of pioglitazone on carotid intima-media thickness and arterial stiffness in type 2 diabetic nephropathy patients. Metabolism. 2004 2004 Oct;53(10):1382-6. PMID: 15375799

97. Nakamura T, Ushiyama C, Shimada N, et al. Comparative effects of pioglitazone, glibenclamide, and voglibose on urinary endothelin-1 and albumin excretion in diabetes patients. J Diabetes Complications. 2000 2000 Sep-Oct;14(5):250-4. PMID: 11113686

98. Bakris G, Viberti G, Weston WM, et al. Rosiglitazone reduces urinary albumin excretion in type II diabetes. J Hum Hypertens. 2003 2003 Jan;17(1):7-12. PMID: 12571611

99. Pfutzner A, Marx N, Lubben G, et al. Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. J Am Coll Cardiol. 2005 2005 Jun 21;45(12):1925-31. PMID: 15963388

100. Tan MH, Johns D, Strand J, et al. Sustained effects of pioglitazone vs. glibenclamide on insulin sensitivity, glycaemic control, and lipid profiles in patients with Type 2 diabetes. Diabet Med. 2004 2004 Aug;21(8):859-66. PMID: 15270789

101. Tan M, Johns D, Gonzalez Galvez G, et al. Effects of pioglitazone and glimepiride on glycemic control and insulin sensitivity in Mexican patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, parallel-group trial. Clin Ther. 2004 2004 May;26(5):680-93. PMID: 15220012

102. Nakamura T, Sugaya T, Kawagoe Y, et al. Effect of pioglitazone on urinary liver-type fatty acid-binding protein concentrations in diabetes patients with microalbuminuria. Diabetes Metab Res Rev. 2006 2006 Sep-Oct;22(5):385-9. PMID: 16506273

103. Shihara N, Kitaoka M, Inagaki N, et al. Randomized controlled trial of single-agent glimepiride and pioglitazone in Japanese patients with type 2 diabetes: A comparative study. J Diabetes Investig. 2011 Oct 7;2(5):391-8. PMID: 24843519.

104. Rosenstock J, Inzucchi SE, Seufert J, et al. Initial combination therapy with alogliptin and pioglitazone in drug-naive patients with type 2 diabetes. Diabetes Care. 2010 Nov;33(11):2406-8. PMID: 20724648.

105. Xu W, Bi Y, Sun Z, et al. Comparison of the effects on glycaemic control and beta-cell function in newly diagnosed type 2 diabetes patients of treatment with exenatide, insulin or pioglitazone: a multicentre randomized parallel-group trial (the CONFIDENCE study). J Intern Med. 2015 Jan;277(1):137-50. PMID: 25039675.

106. Barnett AH, Patel S, Harper R, et al. Linagliptin monotherapy in type 2 diabetes patients for whom metformin is inappropriate: an 18-week randomized, double-blind, placebo-controlled phase III trial with a 34-week active-controlled extension. Diabetes Obes Metab. 2012 Dec;14(12):1145-54. PMID: 22974280.

107. Arjona Ferreira JC, Marre M, Barzilai N, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. Diabetes Care. 2013 May;36(5):1067-73. PMID: 23248197.

108. Scott R, Wu M, Sanchez M, Stein P. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. Int J Clin Pract. 2007 2007 Jan;61(1):171-80. PMID: 17156104

109. Seino Y, Rasmussen MF, Nishida T, Kaku K. Efficacy and safety of the once-daily human GLP-1 analogue, liraglutide, vs glibenclamide monotherapy in Japanese patients with type 2 diabetes. Curr Med Res Opin. 2010 May;26(5):1013-22. PMID: 20199137.

110. Kaku K, Rasmussen MF, Nishida T, Seino Y. Fifty-two-week, randomized, multicenter trial to compare the safety and efficacy of the novel glucagon-like peptide-1 analog liraglutide vs glibenclamide in patients with type 2 diabetes. J Diabetes Investig. 2011 Nov 30;2(6):441-7. PMID: 24843528.

111. Madsbad S, Schmitz O, Ranstam J, et al. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. Diabetes Care. 2004 2004 Jun;27(6):1335-42. PMID: 15161785

112. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009 2009 Feb 7;373(9662):473-81. PMID: 18819705

113. Garber A, Henry RR, Ratner R, et al. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. Diabetes Obes Metab. 2011 Apr;13(4):348-56. PMID: 21205128.

114. Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Diabetes and Endocrinology [serial on the Internet]. 2013; (3): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/599/CN-00915599/frame.html.

115. Suzuki K, Tanaka S, Aoki C, et al. Greater efficacy and improved endothelial dysfunction in untreated type 2 diabetes with liraglutide versus sitagliptin. Dokkyo Journal of Medical Sciences. 2014;41(3):211-20. PMID: **COULD NOT FIND THIS ONE**

116. Leiter LA, Harris SB, Chiasson J-L, et al. Efficacy and safety of Rosiglitazone as monotherapy or in combination with metformin in primary care settings. Can J Diabetes. 2005 2005;29(4):384-92. PMID: **COULD NOT FIND THIS ONE**

117. Kaku K. Efficacy and safety of therapy with metformin plus pioglitazone in the treatment of patients with type 2 diabetes: a double-blind, placebo-controlled, clinical trial. Curr Med Res Opin. 2009 2009 May;25(5):1111-9. PMID: 19309251

118. Scott R, Loeys T, Davies MJ, Engel SS. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. Diabetes Obes Metab. 2008 2008 Sep;10(10):959-69. PMID: 18201203

119. Weissman P, Goldstein BJ, Rosenstock J, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. Curr Med Res Opin. 2005 2005 Dec;21(12):2029-35. PMID: 16368054

120. Bailey CJ, Bagdonas A, Rubes J, et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. Clin Ther. 2005 2005 Oct;27(10):1548-61. PMID: 16330291

121. Gomez-Perez FJ, Fanghanel-Salmon G, Antonio Barbosa J, et al. Efficacy and safety of rosiglitazone plus metformin in Mexicans with type 2 diabetes. Diabetes Metab Res Rev. 2002 2002 Mar-Apr;18(2):127-34. PMID: 11994904

122. Einhorn D, Rendell M, Rosenzweig J, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The Pioglitazone 027 Study Group. Clin Ther. 2000 2000 Dec;22(12):1395-409. PMID: 11192132

123. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. JAMA. 2000 2000 Apr 5;283(13):1695-702. PMID: 10755495

124. Kadoglou NP, Kapelouzou A, Tsanikidis H, et al. Effects of rosiglitazone/metformin fixed-dose combination therapy and metformin monotherapy on serum vaspin, adiponectin and IL-6 levels in drug-naive patients with type 2 diabetes. Exp Clin Endocrinol Diabetes. 2011 Feb;119(2):63-8. PMID: 21031343.

125. Genovese S, Passaro A, Brunetti P, et al. Pioglitazone Randomised Italian Study on Metabolic Syndrome (PRISMA): effect of pioglitazone with metformin on HDL-C levels in Type 2 diabetic patients. J Endocrinol Invest. 2013 Sep;36(8):606-16. PMID: 23511244.

126. DeFronzo RA, Burant CF, Fleck P, et al. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. J Clin Endocrinol Metab. 2012 May;97(5):1615-22. PMID: 22419732.

127. Borges JL, Bilezikian JP, Jones-Leone AR, et al. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naive type 2 diabetes mellitus patients. Diabetes Obes Metab. 2011 Nov;13(11):1036-46. PMID: 21682834.

128. Feinglos M, Dailey G, Cefalu W, et al. Effect on glycemic control of the addition of 2.5 mg glipizide GITS to metformin in patients with T2DM. Diabetes Res Clin Pract. 2005 2005 May;68(2):167-75. PMID: 15860246

129. Garber AJ, Donovan DSJ, Dandona P, et al. Efficacy of glyburide/metformin tablets compared with initial monotherapy in type 2 diabetes. J Clin Endocrinol Metab. 2003 2003 Aug;88(8):3598-604. PMID: 12915642

130. Goldstein BJ, Pans M, Rubin CJ. Multicenter, randomized, double-masked, parallel-group assessment of simultaneous glipizide/metformin as second-line pharmacologic treatment for patients with type 2 diabetes mellitus that is inadequately controlled by a sulfonylurea. Clin Ther. 2003 2003 Mar;25(3):890-903. PMID: 12852706

131. Blonde L, Rosenstock J, Mooradian AD, et al. Glyburide/metformin combination product is safe and efficacious in patients with type 2 diabetes failing sulphonylurea therapy. Diabetes Obes Metab. 2002 2002 Nov;4(6):368-75. PMID: 12406033

132. Marre M, Howlett H, Lehert P, Allavoine T. Improved glycaemic control with metformin-glibenclamide combined tablet therapy (Glucovance) in Type 2 diabetic patients inadequately controlled on metformin. Diabet Med. 2002 2002 Aug;19(8):673-80. PMID: 12147149

133. Garber AJ, Larsen J, Schneider SH, et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. Diabetes Obes Metab. 2002 2002 May;4(3):201-8. PMID: 12047399

134. Hermann LS, Schersten B, Bitzen PO, et al. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care. 1994 1994 Oct;17(10):1100-9. PMID: 7821128

135. Hermann LS, Bitzen PO, Kjellstrom T, et al. Comparative efficacy of metformin and glibenclamide in patients with non-insulin-dependent diabetes mellitus. Diabete Metab. 1991 1991 May;17(1 Pt 2):201-8. PMID: 1936477

136. Charpentier G, Fleury F, Kabir M, et al. Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. Diabet Med. 2001 2001 Oct;18(10):828-34. PMID: 11678974

137. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. The New England journal of medicine. 1995 1995 Aug 31;333(9):541-9. PMID: 7623902

138. Chien HH, Chang CT, Chu NF, et al. Effect of glyburide-metformin combination tablet in patients with type 2 diabetes. J Chin Med Assoc. 2007 2007 Nov;70(11):473-80. PMID: 18063500

139. Forst T, Uhlig-Laske B, Ring A, et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes. Diabet Med. 2010 Dec;27(12):1409-19. PMID: 21059094.

140. Kim HS, Kim DM, Cha BS, et al. Efficacy of glimepiride/metformin fixed-dose combination vs metformin uptitration in type 2 diabetic patients inadequately controlled on low-dose metformin monotherapy: A randomized, open label, parallel group, multicenter study in Korea. Journal of Diabetes Investigation. 2014((Kim H.-S.) Department of Internal Medicine Keimyung University School of Medicine Daegu Korea). PMID: 2542271

141. Ahren B, Johnson SL, Stewart M, et al. HARMONY 3: 104-Week Randomized, Double-Blind, Placebo- and Active-Controlled Trial Assessing the Efficacy and Safety of Albiglutide Compared With Placebo, Sitagliptin, and Glimepiride in Patients With Type 2 Diabetes Taking Metformin. Diabetes Care. 2014 Jun 4. PMID: 24898304.

142. Raz I, Chen Y, Wu M, et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. Curr Med Res Opin. 2008 2008 Feb;24(2):537-50. PMID: 18194595

143. Charbonnel B, Karasik A, Liu J, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care. 2006 2006 Dec;29(12):2638-43. PMID: 17130197

144. DeFronzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care. 2009 Sep;32(9):1649-55. PMID: 19478198.

145. Reasner C, Olansky L, Seck TL, et al. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2011 Jul;13(7):644-52. PMID: 21410627.

146. Yang W, Pan CY, Tou C, et al. Efficacy and safety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Res Clin Pract. 2011 Nov;94(2):217-24. PMID: 21871686.

147. Fonseca V, Zhu T, Karyekar C, Hirshberg B. Adding saxagliptin to extended-release metformin vs. uptitrating metformin dosage. Diabetes Obes Metab. 2012 Apr;14(4):365-71. PMID: 22192246.

148. Yang W, Guan Y, Shentu Y, et al. The addition of sitagliptin to ongoing metformin therapy significantly improves glycemic control in Chinese patients with type 2 diabetes. J Diabetes. 2012 Sep;4(3):227-37. PMID: 22672586.

149. Kadowaki T, Tajima N, Odawara M, et al. Addition of sitagliptin to ongoing metformin monotherapy improves glycemic control in Japanese patients with type 2 diabetes over 52 weeks. J Diabetes Investig. 2013 Mar 18;4(2):174-81. PMID: 24843649.

150. Derosa G, Carbone A, D'Angelo A, et al. Variations in inflammatory biomarkers following the addition of sitagliptin in patients with type 2 diabetes not controlled with metformin. Intern Med. 2013;52(19):2179-87. PMID: 24088749.

151. White JL, Buchanan P, Li J, Frederich R. A randomized controlled trial of the efficacy and safety of twice-daily saxagliptin plus metformin combination therapy in patients with type 2 diabetes and inadequate glycemic control on metformin monotherapy. BMC Endocr Disord. 2014;14(1):17. PMID: 24565221.

152. Ross SA, Rafeiro E, Meinicke T, et al. Efficacy and safety of linagliptin 2.5?mg twice daily versus 5?mg once daily in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, placebo-controlled trial. Curr Med Res Opin [serial on the Internet]. 2012; (9): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/674/CN-00859674/frame.html.

153. Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab [serial on the Internet]. 2013; (12): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/648/CN-00915648/frame.html.

154. Nauck MA, Ellis GC, Fleck PR, et al. Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. Int J Clin Pract. 2009 Jan;63(1):46-55. PMID: 19125992.

155. Taskinen MR, Rosenstock J, Tamminen I, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2011 Jan;13(1):65-74. PMID: 21114605.

156. Rosenstock J, Aggarwal N, Polidori D, et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care. 2012 Jun;35(6):1232-8. PMID: 22492586.

157. Seino Y, Miyata Y, Hiroi S, et al. Efficacy and safety of alogliptin added to metformin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label, long-term extension study. Diabetes Obes Metab. 2012 Oct;14(10):927-36. PMID: 22583697.

158. Lavalle-Gonzalez FJ, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia. 2013 Dec;56(12):2582-92. PMID: 24026211.

159. Nauck M, Weinstock RS, Umpierrez GE, et al. Efficacy and Safety of Dulaglutide Versus Sitagliptin After 52 Weeks in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-5). Diabetes Care. 2014 Apr 17. PMID: 24742660.

160. Wang W, Yang J, Yang G, et al. Efficacy and safety of linagliptin in Asian patients with type 2 diabetes mellitus inadequately controlled by metformin: A multinational 24-week, randomized clinical trial. J Diabetes. 2015 Mar 6. PMID: 25753488.

161. Hermans MP, Delibasi T, Farmer I, et al. Effects of saxagliptin added to sub-maximal doses of metformin compared with uptitration of metformin in type 2 diabetes: the PROMPT study. Curr Med Res Opin. 2012 Oct;28(10):1635-45. PMID: 23020253.

162. Ji L, Zinman B, Patel S, et al. Efficacy and safety of linagliptin co-administered with low-dose metformin once daily versus high-dose metformin twice daily in treatment-naive patients with type 2 diabetes: a double-blind randomized trial. Adv Ther. 2015 Mar;32(3):201-15. PMID: 25805187.

163. Aaboe K, Knop FK, Vilsboll T, et al. Twelve weeks treatment with the DPP-4 inhibitor, sitagliptin, prevents degradation of peptide YY and improves glucose and non-glucose induced insulin secretion in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2010 Apr;12(4):323-33. PMID: 20380653.

164. Haak T, Meinicke T, Jones R, et al. Initial combination of linagliptin and metformin in patients with type 2 diabetes: efficacy and safety in a randomised, double-blind 1-year extension study. Int J Clin Pract. 2013 Dec;67(12):1283-93. PMID: 24118640.

165. Qiu R, Capuano G, Meininger G. Efficacy and safety of twice-daily treatment with canagliflozin, a sodium glucose co-transporter 2 inhibitor, added on to metformin monotherapy in patients with type 2 diabetes mellitus. Journal of Clinical and Translational Endocrinology. 2014;1(2):54-60. PMID: **COULD NOT FIND THIS ONE**

166. Haring HU, Merker L, Seewaldt-Becker E, et al. Empaglif lozin as add-on to metformin in patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014;37(6):1650-9. PMID: 24722494

167. Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet. 2010 Jun 26;375(9733):2223-33. PMID: 20609968.

168. Schumm-Draeger PM, Burgess L, Koranyi L, et al. Twice-daily dapagliflozin co-administered with metformin in type 2 diabetes: a 16-week randomized, placebo-controlled clinical trial. Diabetes Obes Metab. 2015 Jan;17(1):42-51. PMID: 25200570.

169. Bolinder J, Ljunggren O, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab. 2012 Mar;97(3):1020-31. PMID: 22238392.

170. Bailey CJ, Gross JL, Hennicken D, et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013;11:43. PMID: 23425012.

171. Derosa G, Cicero AF, Franzetti IG, et al. Effects of exenatide and metformin in combination on some adipocytokine levels: a comparison with metformin monotherapy. Can J Physiol Pharmacol. 2013 Sep;91(9):724-32. PMID: 23984793.

172. Forst T, Michelson G, Ratter F, et al. Addition of liraglutide in patients with Type 2 diabetes well controlled on metformin monotherapy improves several markers of vascular function. Diabet Med. 2012 Sep;29(9):1115-8. PMID: 22288732.

173. Apovian CM, Bergenstal RM, Cuddihy RM, et al. Effects of exenatide combined with lifestyle modification in patients with type 2 diabetes. Am J Med. 2010 May;123(5):468 e9-17. PMID: 20399326.

174. DeFronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005 May;28(5):1092-100. PMID: 15855572.

175. Hamann A, Garcia-Puig J, Paul G, et al. Comparison of fixed-dose rosiglitazone/metformin combination therapy with sulphonylurea plus metformin in overweight individuals with Type 2 diabetes inadequately controlled on metformin alone. Exp Clin Endocrinol Diabetes. 2008 2008 Jan;116(1):6-13. PMID: 18095238

176. Home PD, Jones NP, Pocock SJ, et al. Rosiglitazone RECORD study: glucose control outcomes at 18 months. Diabet Med. 2007 2007 Jun;24(6):626-34. PMID: 17517066

177. Bakris GL, Ruilope LM, McMorn SO, et al. Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria. J Hypertens. 2006 2006 Oct;24(10):2047-55. PMID: 16957566

178. Umpierrez G, Issa M, Vlajnic A. Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial. Curr Med Res Opin. 2006 2006 Apr;22(4):751-9. PMID: 16684436

179. Derosa G, Gaddi AV, Piccinni MN, et al. Antithrombotic effects of rosiglitazone-metformin versus glimepiride-metformin combination therapy in patients with type 2 diabetes mellitus and metabolic syndrome. Pharmacotherapy. 2005 2005 May;25(5):637-45. PMID: 15899724

180. Garber A, Klein E, Bruce S, et al. Metformin-glibenclamide versus metformin plus rosiglitazone in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Diabetes Obes Metab. 2006 2006 Mar;8(2):156-63. PMID: 16448519

181. Maffioli P, Fogari E, D'Angelo A, et al. Ultrasonography modifications of visceral and subcutaneous adipose tissue after pioglitazone or glibenclamide therapy combined with rosuvastatin in type 2 diabetic patients not well controlled by metformin. Eur J Gastroenterol Hepatol. 2013 Sep;25(9):1113-22. PMID: 23524525.

182. Petrica L, Petrica M, Vlad A, et al. Nephro- and neuroprotective effects of rosiglitazone versus glimepiride in normoalbuminuric patients with type 2 diabetes mellitus: a randomized controlled trial. Wien Klin Wochenschr. 2009;121(23-24):765-75. PMID: 20047115.

183. Comaschi M, Demicheli A, Di Pietro C, et al. Effects of pioglitazone in combination with metformin or a sulfonylurea compared to a fixed-dose combination of metformin and glibenclamide in patients with type 2 diabetes. Diabetes Technol Ther. 2007 2007 Aug;9(4):387-98. PMID: 17705695

184. Schondorf T, Musholt PB, Hohberg C, et al. The fixed combination of pioglitazone and metformin improves biomarkers of platelet function and chronic inflammation in type 2 diabetes patients: results from the PIOfix study. J Diabetes Sci Technol. 2011 Mar;5(2):426-32. PMID: 21527115.

185. Pfutzner A, Schondorf T, Tschope D, et al. PIOfix-study: effects of pioglitazone/metformin fixed combination in comparison with a combination of metformin with glimepiride on diabetic dyslipidemia. Diabetes Technol Ther. 2011 Jun;13(6):637-43. PMID: 21457065.

186. Rigby SP, Handelsman Y, Lai YL, et al. Effects of colesevelam, rosiglitazone, or sitagliptin on glycemic control and lipid profile in patients with type 2 diabetes mellitus inadequately controlled by metformin monotherapy. Endocr Pract. 2010 Jan-Feb;16(1):53-63. PMID: 19789153.

187. Chawla S, Kaushik N, Singh NP, et al. Effect of addition of either sitagliptin or pioglitazone in patients with uncontrolled type 2 diabetes mellitus on metformin: A randomized controlled trial. J Pharmacol Pharmacother. 2013 Jan;4(1):27-32. PMID: 23662021.

188. Bergenstal RM, Wysham C, Macconell L, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet. 2010 Aug 7;376(9739):431-9. PMID: 20580422.

189. DeFronzo RA, Triplitt C, Qu Y, et al. Effects of exenatide plus rosiglitazone on beta-cell function and insulin sensitivity in subjects with type 2 diabetes on metformin. Diabetes Care. 2010 May;33(5):951-7. PMID: 20107105.

190. Arechavaleta R, Seck T, Chen Y, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2011 Feb;13(2):160-8. PMID: 21199268.

191. Forst T, Anastassiadis E, Diessel S, et al. Effect of linagliptin compared to glimepiride on postprandial glucose metabolism, islet cell function, and vascular function parameters in patients with type 2 diabetes mellitus on ongoing metformin treatment. Diabetes Metab Res Rev. 2014 Jan 23. PMID: 24459063.

192. Nauck MA, Meininger G, Sheng D, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007 2007 Mar;9(2):194-205. PMID: 17300595

193. Schernthaner G, Duran-Garcia S, Hanefeld M, et al. Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). Diabetes Obes Metab. 2015 Jul;17(7):630-8. PMID: 25761977.

194. Gallwitz B, Rosenstock J, Rauch T, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet. 2012 Aug 4;380(9840):475-83. PMID: 22748821.

195. Goke B, Gallwitz B, Eriksson J, et al. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. Int J Clin Pract. 2010 Nov;64(12):1619-31. PMID: 20846286.

196. Seck T, Nauck M, Sheng D, et al. Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. Int J Clin Pract. 2010 Apr;64(5):562-76. PMID: 20456211.

197. Del Prato S, Camisasca R, Wilson C, Fleck P. Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study. Diabetes Obes Metab. 2014 Dec;16(12):1239-46. PMID: 25132212.

198. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013 Sep 14;382(9896):941-50. PMID: 23850055.

199. Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care. 2011 Sep;34(9):2015-22. PMID: 21816980.

200. Ridderstrale M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. The Lancet Diabetes and Endocrinology. 2014((Ridderstrale M., mtrd@steno.dk) Steno Diabetes Center, Gentofte, Denmark). PMID: 24948511

201. Leiter LA, Yoon KH, Arias P, et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care. 2015 Mar;38(3):355-64. PMID: 25205142.

202. Zhang H, Zhang X, Hu C, Lu W. Exenatide reduces urinary transforming growth factor-beta1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria. Kidney Blood Press Res. 2012;35(6):483-8. PMID: 22687869.

203. Derosa G, Putignano P, Bossi AC, et al. Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type 2 diabetic patients. Eur J Pharmacol. 2011 Sep;666(1-3):251-6. PMID: 21645507.

204. Yang W, Chen L, Ji Q, et al. Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial(*). Diabetes Obes Metab. 2011 Jan;13(1):81-8. PMID: 21114607.

205. Derosa G, Maffioli P, Salvadeo SA, et al. Exenatide versus glibenclamide in patients with diabetes. Diabetes Technol Ther. 2010 Mar;12(3):233-40. PMID: 20151774.

206. Moon JS, Ha KS, Yoon JS, et al. The effect of glargine versus glimepiride on pancreatic beta-cell function in patients with type 2 diabetes uncontrolled on metformin monotherapy: open-label, randomized, controlled study. Acta Diabetol. 2014 Apr;51(2):277-85. PMID: 24445656.

207. Malone JK, Beattie SD, Campaigne BN, et al. Therapy after single oral agent failure: adding a second oral agent or an insulin mixture? Diabetes Res Clin Pract. 2003 2003 Dec;62(3):187-95. PMID: 14625133

208. Kvapil M, Swatko A, Hilberg C, Shestakova M. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. Diabetes Obes Metab. 2006 2006 Jan;8(1):39-48. PMID: 16367881

209. Rosenstock J, Hansen L, Zee P, et al. Dual Add-on Therapy in Type 2 Diabetes Poorly Controlled With Metformin Monotherapy: A Randomized Double-Blind Trial of Saxagliptin Plus Dapagliflozin Addition Versus Single Addition of Saxagliptin or Dapagliflozin to Metformin. Diabetes Care. 2015 Mar;38(3):376-83. PMID: 25352655.

210. Pratley RE, Nauck M, Bailey T, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet. 2010 Apr 24;375(9724):1447-56. PMID: 20417856.

211. Aschner P, Chan J, Owens DR, et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. Lancet. 2012 Jun 16;379(9833):2262-9. PMID: 22683131.

212. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet. 2010 Jun 26;375(9733):2234-43. PMID: 20609969.

213. Gallwitz B, Bohmer M, Segiet T, et al. Exenatide twice daily versus premixed insulin aspart 70/30 in metformin-treated patients with type 2 diabetes: a randomized 26-week study on glycemic control and hypoglycemia. Diabetes Care. 2011 Mar;34(3):604-6. PMID: 21285388.

214. Robbins DC, Beisswenger PJ, Ceriello A, et al. Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. Clin Ther. 2007 2007 Nov;29(11):2349-64. PMID: 18158076

215. Raskin PR, Hollander PA, Lewin A, et al. Basal insulin or premix analogue therapy in type 2 diabetes patients. Eur J Intern Med. 2007 2007 Jan;18(1):56-62. PMID: 17223044

216. Davies MJ, Thaware PK, Tringham JR, et al. A randomized controlled trial examining combinations of repaglinide, metformin and NPH insulin. Diabet Med. 2007 2007 Jul;24(7):714-9. PMID: 17403126

217. St John Sutton M, Rendell M, Dandona P, et al. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. Diabetes Care. 2002 2002 Nov;25(11):2058-64. PMID: 12401757

218. Derosa G, Cicero AF, Gaddi AV, et al. Long-term effects of glimepiride or rosiglitazone in combination with metformin on blood pressure control in type 2 diabetic patients affected by the metabolic syndrome: a 12-month, double-blind, randomized clinical trial. Clin Ther. 2005 2005 Sep;27(9):1383-91. PMID: 16291411

219. Nauck MA, Del Prato S, Duran-Garcia S, et al. Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus was inadequately controlled with metformin. Diabetes Obes Metab. 2014 Jun 12. PMID: 24919526.

220. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ. 2000 Aug 12;321(7258):412-9. PMID: 10938049.

221. Holman RR, Paul SK, Bethel MA, et al. Long-term follow-up after tight control of blood pressure in type 2 diabetes. The New England journal of medicine. 2008 Oct 9;359(15):1565-76. PMID: 18784091.

222. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005 Jun 27;165(12):1410-9. PMID: 15983291.

223. Malone JK, Kerr LF, Campaigne BN, et al. Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clin Ther. 2004 2004 Dec;26(12):2034-44. PMID: 15823767

224. Malone JK, Bai S, Campaigne BN, et al. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. Diabet Med. 2005 2005 Apr;22(4):374-81. PMID: 15787659

225. Andersson C, Olesen JB, Hansen PR, et al. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. Diabetologia. 2010 Dec;53(12):2546-53. PMID: 20838985.

226. Horsdal HT, Sondergaard F, Johnsen SP, Rungby J. Antidiabetic treatments and risk of hospitalisation with myocardial infarction: a nationwide case-control study. Pharmacoepidemiol Drug Saf. 2011 Apr;20(4):331-7. PMID: 21442682.

227. Mogensen UM, Andersson C, Fosbol EL, et al. Cardiovascular safety of combination therapies with incretin-based drugs and metformin compared with a combination of metformin and sulphonylurea in type 2 diabetes mellitus - a retrospective nationwide study. Diabetes Obes Metab. 2014 May 14. PMID: 24827939.

228. Scheller NM, Mogensen UM, Andersson C, et al. All-cause mortality and cardiovascular effects associated with the DPP-IV inhibitor sitagliptin compared with metformin, a retrospective cohort study on the Danish population. Diabetes, obesity & metabolism. 2014;16(3):231-6. PMID: 24020750

229. Schramm TK, Gislason GH, Vaag A, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J. 2011 Aug;32(15):1900-8. PMID: 21471135.

230. Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 diabetes. Diabet Med. 2005 2005 Apr;22(4):497-502. PMID: 15787679

231. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013 May;36(5):1304-11. PMID: 23230096.

232. Raskin P, Lewin A, Reinhardt R, Lyness W. Twice-daily dosing of a repaglinide/metformin fixed-dose combination tablet provides glycaemic control comparable to rosiglitazone/metformin tablet. Diabetes Obes Metab. 2009 2009 May 19. PMID: 19476470

233. Pantalone KM, Kattan MW, Yu C, et al. The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. Acta Diabetol. 2009 2009 Jun;46(2):145-54. PMID: 19194648

234. Wheeler S, Moore K, Forsberg CW, et al. Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea or rosiglitazone monotherapy. Diabetologia. 2013 Jun 25. PMID: 23797633.

235. Kahler KH, Rajan M, Rhoads GG, et al. Impact of oral antihyperglycemic therapy on all-cause mortality among patients with diabetes in the Veterans Health Administration. Diabetes Care. 2007 2007 Jul;30(7):1689-93. PMID: 17440170

236. Wang CP, Lorenzo C, Espinoza SE. Frailty Attenuates the Impact of Metformin on Reducing Mortality in Older Adults with Type 2 Diabetes. J Endocrinol Diabetes Obes. 2014;2(2). PMID: 25506599.

237. Pantalone KM, Kattan MW, Yu C, et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. Diabetes Obes Metab. 2012 Sep;14(9):803-9. PMID: 22486923.

238. Corrao G, Romio SA, Zambon A, et al. Multiple outcomes associated with the use of metformin and sulphonylureas in type 2 diabetes: a population-based cohort study in Italy. Eur J Clin Pharmacol. 2011 Mar;67(3):289-99. PMID: 21088829.

239. Ferrannini E, Seman L, Seewaldt-Becker E, et al. A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes, obesity & metabolism. 2013;15(8):721-8. PMID: 23398530

240. Stenlof K, Cefalu WT, Kim KA, et al. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Curr Med Res Opin. 2014 Feb;30(2):163-75. PMID: 24073995.

241. Jones TA, Sautter M, Van Gaal LF, Jones NP. Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes. Diabetes Obes Metab. 2003 2003 May;5(3):163-70. PMID: 12681023

242. Prentice JC, Conlin PR, Gellad WF, et al. Capitalizing on prescribing pattern variation to compare medications for type 2 diabetes. Value Health. 2014 Dec;17(8):854-62. PMID: 25498781.

243. Hsiao FY, Huang WF, Wen YW, et al. Thiazolidinediones and cardiovascular events in patients with type 2 diabetes mellitus: a retrospective cohort study of over 473,000 patients using the National Health Insurance database in Taiwan. Drug Saf. 2009 2009;32(8):675-90. PMID: 19591532

244. Brownstein JS, Murphy SN, Goldfine AB, et al. Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records. Diabetes Care. 2010 2010 Mar;33(3):526-31. PMID: 20009093

245. Hung YC, Lin CC, Wang TY, et al. Oral hypoglycaemic agents and the development of non-fatal cardiovascular events in patients with type 2 diabetes mellitus. Diabetes Metab Res Rev. 2013 Nov;29(8):673-9. PMID: 23956007.

246. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med. 2012 Nov 6;157(9):601-10. PMID: 23128859.

247. Stewart MW, Cirkel DT, Furuseth K, et al. Effect of metformin plus roziglitazone compared with metformin alone on glycaemic control in well-controlled Type 2 diabetes. Diabet Med. 2006 2006 Oct;23(10):1069-78. PMID: 16978370

248. Goke B, Gallwitz B, Eriksson JG, et al. Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. Int J Clin Pract. 2013 Apr;67(4):307-16. PMID: 23638466.

249. Hung AM, Roumie CL, Greevy RA, et al. Comparative effectiveness of incident oral antidiabetic drugs on kidney function. Kidney Int. 2012 Apr;81(7):698-706. PMID: 22258320.

250. Masica AL, Ewen E, Daoud YA, et al. Comparative effectiveness research using electronic health records: impacts of oral antidiabetic drugs on the development of chronic kidney disease. Pharmacoepidemiol Drug Saf. 2013 Apr;22(4):413-22. PMID: 23436488.

251. Amador-Licona N, Guizar-Mendoza J, Vargas E, et al. The short-term effect of a switch from glibenclamide to metformin on blood pressure and microalbuminuria in patients with type 2 diabetes mellitus. Arch Med Res. 2000 2000 Nov-Dec;31(6):571-5. PMID: 11257323

252. Hung AM, Roumie CL, Greevy RA, et al. Kidney function decline in metformin versus sulfonylurea initiators: assessment of time-dependent contribution of weight, blood pressure, and glycemic control. Pharmacoepidemiol Drug Saf. 2013 Jun;22(6):623-31. PMID: 23592561.

253. Agarwal R, Saha C, Battiwala M, et al. A pilot randomized controlled trial of renal protection with pioglitazone in diabetic nephropathy. Kidney Int. 2005 2005 Jul;68(1):285-92. PMID: 15954919

254. Lehman DM, Lorenzo C, Hernandez J, Wang CP. Statin use as a moderator of metformin effect on risk for prostate cancer among type 2 diabetic patients. Diabetes Care. 2012 May;35(5):1002-7. PMID: 22456867.

255. van Staa TP, Patel D, Gallagher AM, de Bruin ML. Glucose-lowering agents and the patterns of risk for cancer: a study with the General Practice Research Database and secondary care data. Diabetologia. 2012 Mar;55(3):654-65. PMID: 22127412.

256. Skrivanek Z, Gaydos BL, Chien JY, et al. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). Diabetes Obes Metab. 2014 Apr 25. PMID: 24762094.

257. Derosa G, Franzetti I, Gadaleta G, et al. Metabolic variations with oral antidiabetic drugs in patients with Type 2 diabetes: comparison between glimepiride and metformin. Diabetes Nutr Metab. 2004 2004 Jun;17(3):143-50. PMID: 15334791

258. Wright AD, Cull CA, Macleod KM, Holman RR. Hypoglycemia in Type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications. 2006 2006 Nov-Dec;20(6):395-401. PMID: 17070446

259. Weir MA, Gomes T, Mamdani M, et al. Impaired renal function modifies the risk of severe hypoglycaemia among users of insulin but not glyburide: a population-based nested case-control study. Nephrol Dial Transplant. 2011 Jun;26(6):1888-94. PMID: 20974644.

260. Gupta A, Ahmad Ansari N, Yadav N. Comparative efficacy and safety of sitagliptin and Glimepiride in patients of newly diagnosed type 2 diabetes mellitus. International Journal of Pharmaceutical Sciences Review and Research. 2013;23(2):137-41. PMID: **COULD NOT FIND THIS ONE**

261. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009 2009 Jan;32(1):84-90. PMID: 18931095.

262. Lee YK, Song SO, Kim KJ, et al. Glycemic Effectiveness of Metformin-Based Dual-Combination Therapies with Sulphonylurea, Pioglitazone, or DPP4-Inhibitor in Drug-Naive Korean Type 2 Diabetic Patients. Diabetes Metab J. 2013 Dec;37(6):465-74. PMID: 24404518.

263. Srivastava S, Saxena GN, Keshwani P, Gupta R. Comparing the efficacy and safety profile of sitagliptin versus glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone. J Assoc Physicians India. 2012 Mar;60:27-30. PMID: 22799111.

264. Davies M, Heller S, Sreenan S, et al. Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. Diabetes Care. 2013 May;36(5):1368-76. PMID: 23275363.

265. Derosa G, Gaddi AV, Ciccarelli L, et al. Long-term effect of glimepiride and rosiglitazone on non-conventional cardiovascular risk factors in metformin-treated patients affected by metabolic syndrome: a randomized, double-blind clinical trial. J Int Med Res. 2005 2005 May-Jun;33(3):284-94. PMID: 15938589

266. Kowall B, Rathmann W, Kostev K. Are sulfonylurea and insulin therapies associated with a larger risk of cancer than metformin therapy? A retrospective database analysis. Diabetes Care. 2015 Jan;38(1):59-65. PMID: 25336750.

267. Bolinder J, Ljunggren O, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes, obesity & metabolism. 2014;16(2):159-69. PMID: 23906445

268. Perez-Monteverde A, Seck T, Xu L, et al. Efficacy and safety of sitagliptin and the fixed-dose combination of sitagliptin and metformin vs. pioglitazone in drug-naive patients with type 2 diabetes. Int J Clin Pract. 2011 Sep;65(9):930-8. PMID: 21849007.

269. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA. 1999 1999 Jun 2;281(21):2005-12. PMID: 10359389

270. Kawai T, Funae O, Shimada A, et al. Effects of pretreatment with low-dose metformin on metabolic parameters and weight gain by pioglitazone in Japanese patients with type 2 diabetes. Intern Med. 2008 2008;47(13):1181-8. PMID: 18591838

271. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. United Kingdom Prospective Diabetes Study Group. Ann Intern Med. 1998 1998 Feb 1;128(3):165-75. PMID: 9454524

272. Gallwitz B, Rosenstock J, Patel S, et al. Regardless of the degree of glycaemic control, linagliptin has lower hypoglycaemia risk than all doses of glimepiride, at all time points, over the course of a 2-year trial. Diabetes Obes Metab. 2015 Mar;17(3):276-84. PMID: 25425502.

273. Kahn SE, Zinman B, Lachin JM, et al. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care. 2008 2008 May;31(5):845-51. PMID: 18223031

274. Dormuth CR, Carney G, Carleton B, et al. Thiazolidinediones and fractures in men and women. Arch Intern Med. 2009 2009 Aug 10;169(15):1395-402. PMID: 19667303

275. Schellhase KG, Koepsell TD, Weiss NS. Glycemic control and the risk of multiple microvascular diabetic complications. Fam Med. 2005 Feb;37(2):125-30. PMID: 15690253.

276. Vijan S, Hofer TP, Hayward RA. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. Ann Intern Med. 1997 Nov 1;127(9):788-95. PMID: 9382399.

277. Shyangdan DS, Royle P, Clar C, et al. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews [serial on the Internet]. 2011; (10): Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006423.pub2/abstract.

278. Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: A network meta-analysis. Diabetes, obesity & metabolism. 2012 Sep;14(9):810-20. PMID: 22486990.

279. McIntosh B, Cameron C, Singh SR, et al. Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. Open Med. 2011;5(1):e35-48. PMID: 22046219.

280. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest. 2000 Aug;106(4):473-81. PMID: 10953022.

281. Purnell TS, Joy S, Little E, et al. Patient preferences for noninsulin diabetes medications: a systematic review. Diabetes Care. 2014 Jul;37(7):2055-62. PMID: 24963113.

282. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013 Aug 20;159(4):262-74. PMID: 24026259.

283. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews [serial on the Internet]. 2008; (2): Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006739.pub2/abstract.

284. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991 Jun 26;265(24):3255-64. PMID: 2046107.

285. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998 Sep 12;317(7160):703-13. PMID: 9732337.

286. Wang JG, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. Arch Intern Med. 2000 Jan 24;160(2):211-20. PMID: 10647760.

287. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. The New England journal of medicine. 2001 Jan 4;344(1):3-10. PMID: 11136953.

288. Wu J, Kraja AT, Oberman A, et al. A summary of the effects of antihypertensive medications on measured blood pressure. Am J Hypertens. 2005 Jul;18(7):935-42. PMID: 16053990.

289. Nauman J, Janszky I, Vatten LJ, Wisloff U. Temporal changes in resting heart rate and deaths from ischemic heart disease. JAMA. 2011 Dec 21;306(23):2579-87. PMID: 22187277.

290. Phung OJ, Schwartzman E, Allen RW, et al. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. Diabet Med. 2013 Oct;30(10):1160-71. PMID: 23663156.

291. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: A meta-analysis of randomized clinical trials. Diabetes, obesity & metabolism. 2013 Oct;15(10):938-53. PMID: 23594109.

292. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. The New England journal of medicine. 2007 Jun 14;356(24):2457-71. PMID: 17517853.

293. U.S. Food and Drug Administration. FDA Drug Safety Communication: Updated Risk Evaluation and Mitigation Strategy (REMS) to Restrict Acces to Rosiglitazone-containing Medicines including Avandia, Avandamet, and Avandaryl. 2013; http://www.fda.gov/Drugs/DrugSafety/ucm255005.htm. Accessed 2015 February 26.

294. U.S. Food and Drug Administration. FDA significantly restricts access to the diabetes drug Avandia. 2010; http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226956.htm. Accessed 2015 February 26.

295. U.S. Food and Drug Administration. FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines. 2013; http://www.fda.gov/downloads/Drugs/DrugSafety/UCM381108.pdf. Accessed 2015 February 25.

296. Goossen K, Graber S. Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab. 2012 Dec;14(12):1061-72. PMID: 22519906.

297. Wu D, Li L, Liu C. Efficacy and safety of dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis. Diabetes Obes Metab. 2014 Jan;16(1):30-7. PMID: 23803146.

298. Karagiannis T, Paschos P, Paletas K, et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: Systematic review and meta-analysis. BMJ (Online). 2012;344(7850):17. PMID: 22411919

299. Monami M, Ahren B, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: Ameta-analysis of randomized clinical trials. Diabetes, obesity & metabolism. 2013;15(2):112-20. PMID: 22925682

300. Johansen OE, Neubacher D, von Eynatten M, et al. Cardiovascular safety with linagliptin in patients with type 2 diabetes mellitus: a pre-specified, prospective, and adjudicated meta-analysis of a phase 3 programme. Cardiovasc Diabetol. 2012;11:3. PMID: 22234149.

301. Iqbal N, Parker A, Frederich R, et al. Assessment of the cardiovascular safety of saxagliptin in patients with type 2 diabetes mellitus: pooled analysis of 20 clinical trials. Cardiovasc Diabetol. 2014;13:33. PMID: 24490835.

302. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. The New England journal of medicine. 2013 Oct 3;369(14):1317-26. PMID: 23992601.

303. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine. 2015 Jul 16;373(3):232-42. PMID: 26052984.

304. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. The New England journal of medicine. 2013 Oct 3;369(14):1327-35. PMID: 23992602.

305. Monami M, Dicembrini I, Nardini C, et al. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: A meta-analysis of randomized clinical trials. Diabetes, obesity & metabolism. 2014;16(1):38-47. PMID: 23829656

306. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010;340:b4909. PMID: 20061358.

307. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. The New England journal of medicine. 2009 Oct 29;361(18):1736-47. PMID: 19850703.

308. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med. 2007 Dec 4;147(11):755-65. PMID: 18056659.

309. Franciosi M, Lucisano G, Lapice E, et al. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One. 2013;8(8):e71583. PMID: 23936520.

310. Zhang ZJ, Bi Y, Li S, et al. Reduced risk of lung cancer with metformin therapy in diabetic patients: a systematic review and meta-analysis. Am J Epidemiol. 2014 Jul 1;180(1):11-4. PMID: 24920786.

311. Ferwana M, Firwana B, Hasan R, et al. Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies. Diabet Med. 2013 Sep;30(9):1026-32. PMID: 23350856.

312. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89. PMID: 16214598.

313. Erdmann E, Song E, Spanheimer R, et al. Observational follow-up of the PROactive study: a 6-year update. Diabetes Obes Metab. 2014 Jan;16(1):63-74. PMID: 23859428.

314. U.S. Food and Drug Administration. Incretin Mimetic Drugs for Type 2 Diabetes: Early Communication - Reports of Possible Increased Risk of Pancreatitis and Pre-cancerous Findings of the Pancreas. 2013; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm343805.htm. Accessed 2015 August 1.

315. U.S. Food and Drug Administration. Highlights of Prescribing Information: Victoza (liraglutide [rDNA origin] injection, solution for subcutaneous use. 2011; http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022341s004lbl.pdf. Accessed 2015 March 2.

316. U.S. Food and Drug Administration. Highlights of Prescribing Information: Tanzeum (albiglutide) for injection, for subcutaneous use. 2014; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125431s000lbl.pdf. Accessed 2015 March 2.

317. U.S. Food and Drug Administration. Highlights of Prescribing Information: Bydureon (exenatide extended-release) for injectable suspension. 2015; http://www.fda.gov/safety/medwatch/safetyinformation/ucm400570.htm. Accessed 2015 August 7.

318. U.S. Food and Drug Administration. Trulicity (dulaglutide) Injection, for Subcutaneous Use. 2015; http://www.fda.gov/safety/medwatch/safetyinformation/ucm442202.htm. Accessed 2015 August 7.

319. U.S. Food and Drug Administration. Victoza (liraglutide [rDNA origin]) Injection: REMS - Risk of Thyroid C-cell Tumors, Acute Pancreatitis. 2011; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258826.htm; . Accessed 2015 February 25.

320. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007 Sep 29;370(9593):1129-36. PMID: 17905165.

321. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA. 2007 Sep 12;298(10):1189-95. PMID: 17848653.

322. GlaxoSmithKline. Highlights of Prescribing Information: Avandia (rosiglitazone maleate) tablets. 2014; http://us.gsk.com/products/assets/us_avandia.pdf. Accessed 2015 March 2.

323. Takeda Pharmaceuticals America. Highlights of Prescribing Information: Actos (pioglitazone) tables for oral use. 2013; http://general.takedapharm.com/content/file/pi.pdf?applicationcode=8a9c4571-a123-4477-91deb9cafe7d07e3&filetypecode=actospi. Accessed 2015 March 2.

324. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet. 2015 May 23;385(9982):2067-76. PMID: 25765696.

325. U.S. Food and Drug Administration. FDA Panel Wants New DPP-4 Inhibitor Labels - Cardiovascular data warrant new risk information for saxagliptin and alogliptin, advisers say.; http://www.medpagetoday.com/PublicHealthPolicy/ClinicalTrials/50990. Accessed 2015 July 25, .

326. Clinicaltrials.gov. CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes. 2010; https://clinicaltrials.gov/ct2/show/NCT01243424. Accessed 2015 July 30, .

327. Clinicaltrials.gov. Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA). 2013; https://clinicaltrials.gov/ct2/show/NCT01897532. Accessed 2015 July 30, .

328. NESINA (alogliptin) tablets. 2015; http://general.takedapharm.com/content/file.aspx?FileTypeCode=NESINAPI&cacheRandomizer=f3b08184-5c02-4cd5-a603-466fafb32324. Accessed 2015 August 7.

329. ACTOS (pioglitazone) tablets for oral use. 2013; http://general.takedapharm.com/content/file.aspx?filetypecode=actospi&cacheRandomizer=bd24db50-cfd1-4e08-a5f0-1414e6c0d33a. Accessed 2015 August 7.

330. Brown JB, Pedula K, Barzilay J, et al. Lactic acidosis rates in type 2 diabetes. Diabetes Care. 1998 Oct;21(10):1659-63. PMID: 9773726.

331. Misbin RI, Green L, Stadel BV, et al. Lactic acidosis in patients with diabetes treated with metformin. The New England journal of medicine. 1998 Jan 22;338(4):265-6. PMID: 9441244.

332. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010(4):CD002967. PMID: 20393934.

333. Inzucchi SE, Lipska KJ, Mayo H, et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA. 2014 Dec 24-31;312(24):2668-75. PMID: 25536258.

334. Sethi BK, Viswanathan V, Kumar A, et al. Liraglutide in Clinical Practice: Insights from LEAD Programme. Supplement to JAPI. 2010 June 2010;58:18-22. PMID: **COULD NOT FIND THIS ONE**

335. Franks AS, Lee PH, George CM. Pancreatitis: a potential complication of liraglutide? Ann Pharmacother. 2012 Nov;46(11):1547-53. PMID: 23136352.

336. Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. BMJ. 2014;348:g2366. PMID: 24736555.

337. Wang T, Wang F, Gou Z, et al. Using real-world data to evaluate the association of incretin-based therapies with risk of acute pancreatitis: a meta-analysis of 1,324,515 patients from observational studies. Diabetes Obes Metab. 2015 Jan;17(1):32-41. PMID: 25200423.

338. Karagiannis T, Boura P, Tsapas A. Safety of dipeptidyl peptidase 4 inhibitors: A perspective review. Therapeutic Advances in Drug Safety. 2014;5(3):138-46. PMID: 25083269

339. U.S. Food and Drug Administration. Highlights of Prescribing Information: Byetta (exenatide) Injection. 2014; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021773s036lbl.pdf Accessed 2015 March 2.

340. U.S. Food and Drug Administration. Highlights of Prescribing Information: Victoza (liraglutide). 2013; http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf Accessed 2015 March 2.

341. U.S. Food and Drug Administration. Summary Review: 125469Orig1s000. 2013; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000SumR.pdf Accessed 2015 March 2.

342. U.S. Food and Drug Administration. Janumet (sitagliptin/metformin HCl) tablets. 2013; http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm196610.htm. Accessed 2015 February 25.

343. Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. Arch Intern Med. 2012 Jul 9;172(13):1005-11. PMID: 22688528.

344. Silva PS, Cavallerano JD, Sun JK, et al. Effect of systemic medications on onset and progression of diabetic retinopathy. Nature Reviews Endocrinology. 2010;6(9):494-507. PMID: 20664533

345. Singh S, Segal JB. Thiazolidinediones and macular edema. Archives of Internal Medicine. 2012;172(13):1011-3. PMID: 22688825

346. Kawalec P, Mikrut A, Lopuch S. The safety of dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose cotransporter 2 (SGLT-2) inhibitors added to metformin background therapy in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2014 May;30(4):269-83. PMID: 24829965.

347. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revised label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. 2015; http://www.fda.gov/Drugs/DrugSafety/ucm461449.htm. Accessed 2015 September 16.

348. U.S. Food and Drug Administration. Highlights of Prescribing Information. Invokana (canagliflozin) tablets, for oral use. 2015; http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204042s006lbl.pdf. Accessed 2015 September 16.

349. Erondu N, Desai M, Ways K, Meininger G. Diabetic Ketoacidosis and Related Events in the Canagliflozin Type 2 Diabetes Clinical Program. Diabetes Care. 2015 Jul 22. PMID: 26203064.

350. United States Renal Data System. 2012 Atlas of CKD & ESRD. 2012; http://www.usrds.org/atlas12.aspx. Accessed 2015 March 2.

351. Centers for Disease Control and Prevention. Diabetic Retinopathy. 2015; http://www.cdc.gov/visionhealth/pdf/factsheet.pdf Accessed 2015 March 2.

352. Centers for Disease Control and Prevention. New Diabetes Atlas. 2014; http://www.cdc.gov/diabetes/data/. Accessed 2015 February 27.

353. The Henry J. Kaiser Family Foundation. Number of Diabetes Deaths per 100,000 Population by Race/Ethnicity. 2015; http://kff.org/other/state-indicator/diabetes-death-rate-by-raceethnicity/ Accessed 2015 February 27.

354. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. Ann Intern Med. 2014 Apr 15;160(8):517-25. PMID: 24733192.

355. Wong HK, Ong KL, Cheung CL, Cheung BM. Utilization of glucose, blood pressure, and lipid lowering medications among people with type II diabetes in the United States, 1999-2010. Ann Epidemiol. 2014 Jul;24(7):516-21 e1. PMID: 24935464.

356. Qaseem A, Humphrey LL, Sweet DE, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31. PMID: 22312141.

357. Bristol-Myers Squibb. GLUCOPHAGE® (metformin hydrochloride) Tablets. GLUCOPHAGE® XR (metformin hydrochloride) Extended-Release Tablets. http://packageinserts.bms.com/pi/pi_glucophage_xr.pdf. Accessed 2015 July 30, .

358. Bailey RA, Wang Y, Zhu V, Rupnow MF. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: Improving Global Outcomes (KDIGO) staging. BMC Res Notes. 2014;7:415. PMID: 24990184.

359. Turner R, Murchison L, Wright AD, et al. United Kingdom prospective diabetes study 24: A 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med. 1998 1998;128(3):165-75. PMID: 9454524.

360. U.K. prospective diabetes study. II. Reduction in HbA1c with basal insulin supplement, sulfonylurea, or biguanide therapy in maturity-onset diabetes. A multicenter study. Diabetes. 1985 Aug;34(8):793-8. PMID: 2862087.

361. United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ. 1995 Jan 14;310(6972):83-8. PMID: 7833731.

362. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. The New England journal of medicine. 2008 Jun 12;358(24):2560-72. PMID: 18539916.

363. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA. 2008 Apr 2;299(13):1561-73. PMID: 18378631.

364. Buse JB, Henry RR, Han J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care. 2004 Nov;27(11):2628-35. PMID: 15504997.

365. Blonde L, Klein EJ, Han J, et al. Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. Diabetes Obes Metab. 2006 Jul;8(4):436-47. PMID: 16776751.

366. Zinman B, Hoogwerf BJ, Duran Garcia S, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2007 Apr 3;146(7):477-85. PMID: 17404349.

367. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009 Jul 4;374(9683):39-47. PMID: 19515413.

368. Marre M, Shaw J, Brandle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med. 2009 Mar;26(3):268-78. PMID: 19317822.

369. Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009 Jul;32(7):1224-30. PMID: 19289857.

370. Li T, Hutfless S, Scharfstein DO, et al. Standards should be applied in the prevention and handling of missing data for patient-centered outcomes research: a systematic review and expert consensus. J Clin Epidemiol. 2014 Jan;67(1):15-32. PMID: 24262770.

371. Patorno E, Patrick AR, Garry EM, et al. Observational studies of the association between glucose-lowering medications and cardiovascular outcomes: addressing methodological limitations. Diabetologia. 2014 Nov;57(11):2237-50. PMID: 25212258.

Abbreviations

ADOPT = A Diabetes Outcome Progression Trial
AHRQ = Agency for Healthcare Research and Quality
BMI = body mass index
CARMELINA = Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus
CAROLINA = Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes
CER = comparative effectiveness reviews
CI = confidence interval
CVD = cardiovascular disease
DPP-4 inhibitors = dipeptidyl-peptidase-4 inhibitors
EHC = Effective Health Care
EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care;
FDA = Food and Drug Administration
GI = gastrointestinal
GLP-1 receptor agonists = glucagon-like peptide-1 receptor agonists
HbA1c = hemoglobin A1c
HR = hazard ratio
LEAD = Liraglutide Effect and Action in Diabetes
MeSH = medical subject headings
OR = odds ratio
PROactive = PROspective pioglitAzone Clinical Trial In macroVascular Events
RCT = randomized controlled trial
RECORD = Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes
RR = risk ratio
SAVOR-TIMI = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction
SGLT-2 inhibitors = sodium glucose co-transporter 2 inhibitors
SOE = Strength of evidence
TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin
TEP = technical expert panel
UKPDS = United Kingdom Prospective Diabetes Study
UTI = urinary tract infection

Appendix A. Detailed Electronic Database Search Strategies

PubMed Strategy

Search	String
#1	(“diabetes mellitus, type 2”[mh] or (diabet*[tiab] and (“non-insulin dependent”[tiab] or type-2[tiab] or “type II”[tiab] or “type 2”[tiab]))) AND (“metformin”[mh] or “thiazolidinediones”[mh] or “glipizide”[mh] or “glyburide”[mh] or “Dipeptidyl-Peptidase IV Inhibitors”[mh] or “Glucagon-Like Peptide 1”[mh] or biguanide*[tiab] or metformin[tiab] or thiazolidinedione*[tiab] or pioglitazone[tiab] or rosiglitazone[tiab] or sulfonylurea*[tiab] or sulphonylurea*[tiab] or glipizide[tiab] or glyburide[tiab] or glimepiride[tiab] or glibenclamide[tiab] or “insulin secretagogues”[tiab] or sitagliptin*[tiab] or saxagliptin*[tiab] or dpp-4[tiab] or dpp-iv[tiab] or liraglutide[tiab] or exenatide[tiab]) NOT (animal[mh] NOT human[mh]) NOT (letter[pt] or comment[pt] or editorial[pt]) AND (("2009/04/01"[edat] : "2014/07/11"[edat]))
#2	(“diabetes mellitus, type 2”[mh] or (diabet*[tiab] and (“non-insulin dependent”[tiab] or type-2[tiab] or “type II”[tiab] or “type 2”[tiab]))) AND (linagliptin*[tiab] or alogliptin*[tiab] or albiglutide*[tiab] or dulaglutide*[tiab] or "sodium-glucose co-transporter 2 inhibitors”[tiab] or “sodium-glucose co-transporter 2 inhibitor” [tiab] or “SGLT-2” [tiab] or “canagliflozin”[tiab] or “dapagliflozin”[tiab]) NOT (animal[mh] NOT human[mh]) NOT (letter[pt] or comment[pt] or editorial[pt])
#3	(“diabetes mellitus, type 2”[mh] or (diabet*[tiab] and (“non-insulin dependent”[tiab] or type-2[tiab] or “type II”[tiab] or “type 2”[tiab]))) AND (empagliflozin*[tiab]) NOT (animal[mh] NOT human[mh]) NOT (letter[pt] or comment[pt] or editorial[pt])

EMBASE Strategy

Search	String
#1	('non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus' or (diabet*:ti,ab and (‘non-insulin dependent’:ti,ab or type-2:ti,ab or ‘type II’:ti,ab or ‘type 2’:ti,ab))) AND ('thiazolidinedione'/exp or 'rosiglitazone'/exp or 'pioglitazone'/exp or 'glipizide'/exp or 'glyburide'/exp or ‘glimepiride’/exp or 'metformin'/exp or ‘sitagliptin’/exp or thiazolidinedione*:ti,ab or pioglitazone:ti,ab or rosiglitazone:ti,ab or sulfonylurea*:ti,ab or sulphonylurea*:ti,ab or glipizide:ti,ab or glyburide:ti,ab or glimepiride:ti,ab or glibenclamide:ti,ab or biguanide*:ti,ab or metformin:ti,ab or ‘insulin secretagogues’:ti,ab or ‘Dipeptidyl-Peptidase IV Inhibitor’/de or saxagliptin/exp or saxagliptin*:ti,ab or sitagliptin/exp or sitagliptin*:ti,ab or dpp-4:ti,ab or dpp-iv:ti,ab or exenatide/exp or exenatide:ti,ab or liraglutide/exp or liraglutide:ti,ab) NOT ([animals]/lim NOT [humans]/lim) NOT (letter:it or comment:it or editorial:it) AND [2009-2014]/py
#2	('non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus' or (diabet*:ti,ab and (‘non-insulin dependent’:ti,ab or type-2:ti,ab or ‘type II’:ti,ab or ‘type 2’:ti,ab))) AND (linagliptin/exp or linagliptin*:ti,ab or alogliptin/exp or alogliptin*:ti,ab or albiglutide/exp or albiglutide*:ti,ab or dulaglutide/exp or dulaglutide*:ti,ab or ‘sodium glucose cotransporter 2 inhibitor’/de or ‘sodium-glucose co-transporter 2 inhibitors’:ti,ab or ‘sodium-glucose co-transporter 2 inhibitor’:ti,ab or ‘sodium glucose cotransporter 2 inhibitors’:ti,ab or ‘sodium glucose cotransporter 2 inhibitor’:ti,ab or ‘SGLT-2”:ti,ab or canagliflozin/exp or canagliflozin:ti,ab or dapagliflozin/exp or dapagliflozin:ti,ab) NOT ([animals]/lim NOT [humans]/lim) NOT (letter:it or comment:it or editorial:it)
#3	('non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus' or (diabet*:ti,ab and (‘non-insulin dependent’:ti,ab or type-2:ti,ab or ‘type II’:ti,ab or ‘type 2’:ti,ab))) AND (empagliflozin/exp or empagliflozin*:ti,ab) NOT ([animals]/lim NOT [humans]/lim) NOT (letter:it or comment:it or editorial:it)

Cochrane Strategy

Search	String
#1	((diabetes near type-2):ti,ab,kw or (diabet*:ti,ab,kw and ("non-insulin dependent":ti,ab,kw or type-2:ti,ab,kw or "type II":ti,ab,kw or "type 2":ti,ab,kw))) AND (thiazolidinedione*:ti,ab,kw or pioglitazone:ti,ab,kw or rosiglitazone:ti,ab,kw or sulfonylurea*:ti,ab,kw or sulphonylurea*:ti,ab,kw or glipizide:ti,ab,kw or glyburide:ti,ab,kw or glimepiride:ti,ab,kw or glibenclamide:ti,ab,kw or biguanide*:ti,ab,kw or metformin:ti,ab,kw or "insulin secretagogues":ti,ab,kw or "Dipeptidyl-Peptidase IV Inhibitors":ti,ab,kw or saxagliptin*:ti,ab,kw or sitagliptin*:ti,ab,kw or liraglutide:ti,ab,kw or exenatide:ti,ab,kw) Publication Year from 2009 to 2014
#2	((diabetes near type-2):ti,ab,kw or (diabet*:ti,ab,kw and ("non-insulin dependent":ti,ab,kw or type-2:ti,ab,kw or "type II":ti,ab,kw or "type 2":ti,ab,kw))) AND (linagliptin*:ti,ab,kw or alogliptin*:ti,ab,kw or albiglutide*:ti,ab,kw or dulaglutide*:ti,ab,kw or 'sodium-glucose co-transporter 2 inhibitors':ti,ab,kw or 'sodium-glucose co-transporter 2 inhibitor':ti,ab,kw or 'sodium glucose cotransporter 2 inhibitors':ti,ab,kw or 'sodium glucose cotransporter 2 inhibitor':ti,ab,kw or 'SGLT-2':ti,ab,kw or canagliflozin:ti,ab,kw or dapagliflozin:ti,ab,kw)
#3	((diabetes near type-2):ti,ab,kw or (diabet*:ti,ab,kw and ("non-insulin dependent":ti,ab,kw or type-2:ti,ab,kw or "type II":ti,ab,kw or "type 2":ti,ab,kw))) AND (empagliflozin*:ti,ab,kw)

Appendix B. Forms

Title Review

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Does this article POTENTIALLY apply to any of our key questions? Yes No

- Metformin
- TZDs (rosiglitazone, pioglitazone)
- Sulfonylureas (glyburide, glibenclamide, glipizide, glimepiride)
- DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)
- SGLT2 inhibitors (dapagliflozin, canagliflozin)
- GLP1 agonists (exenatide, liraglutide, albiglutide, dulaglutide)

Submit Form and go to or Skip to Next

Abstract Review

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

BACKGROUND: Skateboarding has been a popular sport among teenagers even with its attendant associated risks. The literature is packed with articles regarding the perils of skateboards. Is the skateboard as dangerous as has been portrayed?

METHODS: This was a retrospective study conducted over a 5 year period. All skateboard related injuries seen in the Orthopaedic unit were identified and data collated on patient demographics, mechanism & location of injury, annual incidence, type of injury, treatment needed including hospitalisation.

RESULTS: We encountered 50 patients with skateboard related injuries. Most patients were males and under the age of 15. The annual incidence has remained low at about 10. The upper limb was predominantly involved with most injuries being fractures. Most injuries occurred during summer. The commonest treatment modality was plaster immobilisation. The distal radius was the commonest bone to be fractured. There were no head & neck injuries, open fractures or injuries requiring surgical intervention.

CONCLUSION: Despite its negative image among the medical fraternity, the skateboard does not appear to be a dangerous sport with a low incidence and injuries encountered being not severe. Skateboarding should be restricted to supervised skateboard parks and skateboarders should wear protective gear. These measures would reduce the number of skateboarders injured in motor vehicle collisions, reduce the personal injuries among skateboarders, and reduce the number of pedestrians injured in collisions with skateboarders.

Submit Form and go to or Skip to Next

Diabetes Medications Update-3
Abstract Review Form

1. **Exclude** article because (check any that apply):

- ☐ Exclude, but pull for **handsearching** (e.g., systematic review article that applies to key question)
- ☐ No **original data** (e.g., review article, commentary, or editorial)
- ☐ No **human** data reported (e.g., evaluated outcomes in animals only)
- ☐ No subjects **≥18 years of age**
- ☐ No subjects with **type 2 diabetes mellitus**, non-insulin dependent diabetes mellitus (NIDDM), or adult-onset diabetes (e.g. exclude if only type 1 diabetes, MODY, gestational diabetes)
- ☐ No **concurrent control or comparison group** (e.g., case series or case report or pre-post design; note: that case-control studies should be included)
- ☐ Does not have a **drug comparison of interest** (see below)
- ☐ Does not evaluate an **FDA-approved formulation** (e.g., transdermal or sublingual)
- ☐ Followup less than **90 days or 3 months**
- ☐ **Does not apply** to any of the key questions
- ☐ Other reason for exclusion (specify:)
- ☐ **Placebo-controlled trial** where patients are not on background oral diabetes medications

2. **Include or unclear** so include to pull full article

- ☐ Include/unclear
- ☐ Pooled analysis

Priority Medication Comparisons Included for Each Key Question*

	Main Intervention	Comparisons
Monotherapy as main intervention	Metformin	• Placebo • Thiazolidinediones • Sulfonylureas • DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists • Combination of metformin plus thiazolidinedione • Combination of metformin plus sulfonylurea • Combination of metformin plus DPP-4 inhibitor • Combination of metformin plus SGLT2 inhibitor • Combination of metformin plus GLP-1 agonist
	Thiazolidinedione (rosiglitazone, pioglitazone)	• Placebo • Another thiazolidinedione • Sulfonylureas • DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists
	Sulfonylurea (glyburide, glibenclamide, glipizide, glimepiride)	• Placebo • DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists
	DPP-4 inhibitor (sitagliptin, saxagliptin, linagliptin, alogliptin)	• Placebo • Another DPP-4 inhibitor • SGLT2 inhibitors • GLP-1 agonists
	SGLT2 inhibitor (dapagliflozin, canagliflozin, empagliflozin)	• Placebo • Another SGLT2 inhibitors • GLP-1 agonists
	GLP-1 agonists (exenatide, liraglutide, albiglutide, dulaglutide)	• Placebo • Another GLP-1 agonists
Combination therapy as main intervention	Combination of metformin plus (thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 agonist or basal insulin [insulin glargine, insulin detemir, neutral protamine Hagedorn (NPH) insulin] or premixed insulin [NPH/regular 50/50, NPH/regular 70/30, insulin lispro 50/50, insulin lispro 75/25, insulin aspart 70/30])	• Combination of metformin plus (thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 agonist or basal insulin or premixed insulin)

* Do not include if only comparison is with insulin only or with triple combination therapy.

List of fixed-dose combinations to include:
- Metformin/rosiglitazone (Avandamet)
- Metformin/pioglitazone (Actoplus Met)
- Metformin/glipizide (Metaglip)
- Metformin/glyburide (Glucovance)
- Metformin/saxagliptin (Kombiglyze XR)
- Metformin/linagliptin (Jentadueto)
- Metformin/sitagliptin (Janumet)
- Metformin/alogliptin (Kazano)

3. Comments

Submit Form and go to or Skip to Next

Article Review

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Diabetes Medications Update-3
Article Review Form

MAJOR EXCLUSION CRITERIA

1) Exclude article because (check any that apply):

- ☐ Exclude, but pull for **handsearching** (e.g., systematic review article that applies to key question)
- ☐ No **original** data (e.g., review article, commentary, or editorial)
- ☐ Meeting abstract
- ☐ No **human** data reported (e.g., evaluated outcomes in animals only)
- ☐ No subjects **≥18 years of age**
- ☐ No subjects with **type 2 diabetes mellitus**, non-insulin dependent diabetes mellitus (NIDDM), or adult-onset diabetes (e.g. exclude if only type 1 diabetes, MODY, gestational diabetes) or no stratification of results by type of diabetes
- ☐ Does not meet any of the **study design criteria** listed in table 1
- ☐ Does not have a **drug comparison of interest** in table 2
- ☐ Only a **placebo-controlled comparison** (please make sure that they are not on background metformin which could make it a comparison of interest in table 2)
- ☐ Does not evaluate an **FDA-approved formulation** (e.g., transdermal or sublingual)
- ☐ Does not specify **background medications** or no stratification of results by treatment (and for RCTS: no stratified randomization by background medications)
- ☐ No **outcome** of interest
- ☐ Followup less than **3 months or 90 days or 12 weeks**
- ☐ Conducted in a population where everyone is required to have at least one of the following **comorbid conditions** [i.e., end-stage liver disease (e.g., cirrhosis); end-stage renal disease (e.g., stage 5 or dialysis); cancer; or new onset diabetes after transplant; recent cardiovascular event within 3 months (e.g., acute coronary syndrome, acute myocardial infarction, post-CABG, or with drug-eluting stents)]. **(specify comorbid condition):**
- ☐ **Does not apply** to any of the key questions
- ☐ Other (specify):
- ☐ Not written in English
- ☐ Head-to-head intraclass comparison that is NOT rosiglitazone vs. pioglitazone

NON-RANDOMIZED STUDIES (no need to answer if excluded in Q1)

2) Does the article describe a NON-RANDOMIZED STUDY?

Select an Answer

INCLUSION

7) Include article for data abstraction

- ☐ Include
- ☐ do not use
- ☐ Include but comparison of interest is dulaglutide or glargine u300 only
- ☐ Pooled analysis that meets all the inclusion criteria
- ☐ Meets inclusion criteria and is related to another article (enter reference number)

Comments (limit 250 characters)

Table 1. Study design criteria

Key Question	Study design criteria	Comparison limitations
KQ1 - Intermediate outcomes: • HbA1c • Weight • Systolic blood pressure	Include only if: • RCT	HbA1c • Not metformin vs. sulfonylurea Weight • Not metformin vs. thiazolidinedione • Not metformin vs. sulfonylurea Systolic blood pressure • Only for comparisons with SGLT-2 inhibitors or GLP-1 agonists
KQ2 - Long-term clinical outcomes • All-cause mortality • Cardiovascular and cerebrovascular morbidity and mortality • Retinopathy • Nephropathy • Neuropathy	Include only if • RCT • non-randomized clinical trial • cohort with a comparison group, or • case-control study	Include for all comparisons
KQ3 - Adverse events • Liver injury • Severe lactic acidosis • Pancreatitis • Hypoglycemia • Congestive heart failure	Include only if • RCT • non-randomized clinical trial • cohort with a comparison group, or • case-control study	Urinary tract infections, impaired renal function, genital mycotic infections, fracture, volume depletion • Only for comparisons with SGLT-2 inhibitors Heart rate increase • Only for comparisons with SGLT-2 inhibitors or GLP-1 agonists

• Cancer • Severe allergic reactions • Macular edema or decreased vision • Gastrointestinal side effects • Urinary tract infections • Impaired renal function • Genital mycotic infections • Fracture • Volume depletion • Heart rate increase		
KQ4 – Subgroups • Age • Sex • Race/ethnicity • BMI	Follow study design criteria for outcomes as stated above	Follow comparison limitations as stated above

Table 2. Priority Medication Comparisons Included for Each Key Question*

	Main Intervention	Comparisons
Monotherapy as main intervention	Metformin	• Thiazolidinediones • Sulfonylureas • DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists • Combination of metformin plus thiazolidinedione • Combination of metformin plus sulfonylurea • Combination of metformin plus DPP-4 inhibitor • Combination of metformin plus SGLT2 inhibitor • Combination of metformin plus GLP-1 agonist
	Thiazolidinedione (rosiglitazone, pioglitazone)	• Another thiazolidinedione • Sulfonylureas • DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists
	Sulfonylurea (glyburide, glibenclamide, glipizide, glimepiride)	• DPP-4 inhibitors • SGLT2 inhibitors • GLP-1 agonists
	DPP-4 inhibitor (sitagliptin, saxagliptin, linagliptin, alogliptin)	• Another DPP-4 inhibitor • SGLT2 inhibitors • GLP-1 agonists
	SGLT2 inhibitor (dapagliflozin, canagliflozin, empagliflozin)	• Another SGLT2 inhibitor • GLP-1 agonists
	GLP-1 agonists (exenatide, liraglutide, albiglutide, dulaglutide)	• Another GLP-1 agonist
Combination therapy as main intervention	Combination of metformin plus (thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 agonist or basal insulin [insulin glargine, insulin detemir, neutral protamine Hagedorn (NPH) insulin] or premixed insulin [NPH/regular 50/50, NPH/regular 70/30, insulin lispro 50/50, insulin lispro 75/25, insulin aspart 70/30])	• Combination of metformin plus (thiazolidinedione or sulfonylurea or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 agonist or basal insulin or premixed insulin)

* Do not include if only comparison is with insulin only or with triple combination therapy.
List of fixed-dose combinations to include:
• Metformin/rosiglitazone (Avandamet)
• Metformin/pioglitazone (Actoplus Met)
• Metformin/glipizide (Metaglip)
• Metformin/glyburide (Glucovance)
• Metformin/saxagliptin (Kombiglyze XR)
• Metformin/linagliptin (Jentadueto)
• Metformin/sitagliptin (Janumet)
• Metformin/alogliptin (Kazano)

Submit Form and go to or Skip to Next

Study Design

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Diabetes Medications
Study Design Form

Fill out this form for all included studies.

1. In what country does the study occur? **(check all that apply)**

- ☐ United States
- ☐ Canada
- ☐ United Kingdom
- ☐ Japan
- ☐ Multinational Europe
- ☐ Multi-continent
- ☐ Other (specify):
- ☐ Not reported

2. What study design is used? **(check only one response)**

Select an Answer

3. Select trial type **(check all that apply)**

- ☐ Parallel arms
- ☐ Factorial design
- ☐ Crossover design
- ☐ Other (specify):
- ☐ None of the above apply to the trial/Not applicable (not a trial)

4. Was there a run-in period (i.e., a period of observation prior to randomization, including wash-out periods)? **(check only one response)**

Select an Answer

6. Was there pharmaceutical support or involvement (funding of study, co-authorship, or drug given for free) of the study? **(check only one response)**

Select an Answer

7. Study enrollment period (preferred) or dates of study. **Enter 4-digit year for start, end or both years.**

- ☐ Start year:
- ☐ End year:
- ☐ Neither year reported

8. For RCTs and non-randomized trials, what was the total intended followup duration?	9. Specify units: **(check only one response)**
○ Duration: ○ Not reported ○ Not applicable Clear Response	Select an Answer
10. For cohort studies, what was the mean/median followup duration?	11. Specify units: **(check only one response)**
Select an Answer	Select an Answer

12. Was a subgroup of interest (age, gender, race, obesity/BMI) mentioned in the methods or reported in the results?

Select an Answer

Study Population Questions

14. What was the source(s) of the population from which subjects were enrolled in the study? **(check all that apply)**

- ☐ Inpatient/hospital
- ☐ Outpatient: primary care
- ☐ Outpatient: subspecialty care setting
- ☐ Community
- ☐ Other (specify):
- ☐ Not reported
- ☐ Administrative database

15. **If an administrative database was used, please answer. Otherwise skip.**
Name of database (e.g., MarketScan, VA, Denmark):

16. **In an administrative database was used, please answer. Otherwise skip.**
Databases used **(check all that apply)**:

- [ ] Inpatient diagnosis/procedures
- [ ] Outpatient diagnosis/procedures
- [ ] Inpatient pharmacy records
- [ ] Outpatient pharmacy records
- [ ] Cancer registry
- [ ] Death registry
- [ ] Other (specify):

17. What was the total number at randomization or cohort inception?

- [ ] N:
- [ ] Not reported

18. Please select and specify the exclusion criteria. Any inclusion criteria should be entered as exclusion criteria e.g. if the inclusion criteria is type 2 diabetes, the exclusion criteria would be no type 2 diabetes.

- [ ] Age (specify):
- [ ] HbA1c > (specify):
- [ ] HbA1c < (specify):
- [ ] BMI or weight (specify):
- [ ] Duration of diabetes (e.g., number of years or newly diagnosed diabetes) (specify):
- [ ] Prior use of any diabetes treatment
- [ ] Prior or current use of insulin
- [ ] Prior or current use of study drug
- [ ] Male
- [ ] Female
- [ ] Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT))
- [ ] Any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance)
- [ ] History of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina); DO NOT MARK IF RECENT ACUTE EVENT IN PAST 6 MONTHS
- [ ] Contraindication or history of intolerance to metformin
- [ ] Neuropathy
- [ ] Retinopathy
- [ ] Pregnant
- [ ] Nursing
- [ ] Not using adequate contraception
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Not reported

19. Does the study have a registered protocol?

- [ ] Yes (enter registration number)
- [ ] No

Clear Response

20. Does the study reference a protocol?

- [ ] Yes (specify reference number)
- [ ] No

Clear Response

21. Comments **(limit 250 characters)**

22. Comments **(limit 250 characters)**

23. Comments **(limit 250 characters)**

Submit Form and go to or Skip to Next

Intervention Form

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Oral Diabetes Medications Update
Intervention Form

Instructions:
1) Complete this form for all RCT's, cohort studies, and cross-over studies. Do not use this form for case-control studies.
2) For cross-over studies, please record each portion of the crossover as a separate comparison
3) Please use "Case Control Intervention and Outcomes Form" for case-control studies

1. Specify the intervention/exposure for this form: **(Mandatory question; please check one)**

Select an Answer

For monotherapy comparisons where the main intervention is using a single drug, complete the first row only.
For combination comparisons, complete the first row for metformin, and complete the second row for the additional drug.
Only abstract clinically relevant doses.

Intervention (Select one; interventions listed in order of priority)	**Dosing**	**Total daily dose after run-in** (include units; OK to calculate if not explicitly stated) Fill in all dosing information.
○ Metformin **TZDs** ○ Rosiglitazone ○ Pioglitazone ○ Any in the TZD class **Sulfonylureas** ○ Glyburide ○ Glibenclamide ○ Glipizide ○ Glimepiride ○ SU not specified **DPP-4 Inhibitors** ○ Sitagliptin ○ Saxagliptin ○ Linagliptin ○ Alogliptin ○ Any in the DPP-4 inhibitor class **SGLT-2 inhibitors** ○ Dapagliflozin ○ Canagliflozin ○ Empagliflozin ○ Any in the SGLT-2 inhibitor class **GLP-1 agonist** ○ Exenatide ○ Liraglutide ○ Albiglutide ○ Dulaglutide ○ Any in the GLP-1 agonist class Clear Response	○ Fixed ○ Titrated ○ Not specified Clear Response	4. Dosing information ☐ Fixed dose (specify): ☐ Mean daily dose recorded during study (specify): ☐ Median daily dose recorded during study (specify): ☐ Maximum titration dose (specify): ☐ Other (specify): ☐ Not specified/unclear
5. Complete this row ONLY if another drug is added on to metformin. Additional drug (specify): **TZDs** ○ Rosiglitazone ○ Pioglitazone ○ Any in the TZD class **Sulfonylureas** ○ Glyburide ○ Glibenclamide ○ Glipizide ○ Glimepiride ○ SU not specified **DPP-4 Inhibitors** ○ Sitagliptin ○ Saxagliptin ○ Linagliptin ○ Alogliptin ○ Any in the DPP-4 inhibitor class **SGLT-2 inhibitors** ○ Dapagliflozin ○ Canagliflozin ○ Empagliflozin ○ Any in the SGLT-2 inhibitor class **GLP-1 agonist**	○ Fixed ○ Titrated ○ Not specified Clear Response	7. Dosing information ☐ Fixed dose (specify): ☐ Mean daily dose recorded during study (specify): ☐ Median daily dose recorded during study (specify): ☐ Maximum titration dose (specify): ☐ Other (specify): ☐ Not specified/unclear

○ Exenatide ○ Liraglutide ○ Albiglutide ○ Dulaglutide ○ Any in the GLP-1 agonist class **Basal insulin** ○ Insulin glargine ○ NPH ○ Insulin detemir ○ Any basal insulin **Premixed insulin** ○ NPH/regular 70/30 ○ Insulin aspart 70/30 ○ Insulin lispro 75/25 ○ Insulin lispro 50/50 ○ Any premixed insulin Clear Response		
8. Indicate if placebo was provided ○ Placebo Clear Response		

Rescue therapy

9. Was rescue therapy used in this arm? Rescue therapy includes additional pharmacologic therapies that are added to the study intervention.

Select an Answer

12. Comments **(limit 250 characaters)**

13. Comments **(limit 250 characaters)**

14. Comments **(limit 250 characaters)**

Submit Form and go to or Skip to Next

Population Characteristics

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Oral Diabetes Medications Update
Population Form – Baseline Characteristics

Instructions:
1) Use this form for all RCTs, cohort studies, and cross-over studies. Do NOT use this form for case-control studies.
2) For cross-over studies, please record each portion of the crossover as a separate comparison
3) Please use "Case Control Intervention and Outcomes Form" for case-control studies.
4) Only enter data for the first measure that you are able to for each row.

	Main intervention	Comparison A	Comparison B
Total N at enrollment (i.e., at randomization or at beginning of exposure period) ○ Total N not reported Clear Response			
N for baseline characteristics ○ N for baseline characteristics not reported Clear Response			
Age ○ Age not reported Clear Response	☐ Mean ☐ Median ☐ Range ☐ Other, only age categories reported	☐ Mean ☐ Median ☐ Range ☐ Other, only age categories reported	☐ Mean ☐ Median ☐ Range ☐ Other, only age categories rep
Male ○ Male not reported Clear Response	☐ %: ☐ N:	☐ %: ☐ N:	☐ %: ☐ N:
Race/Ethnicity ○ Race/ethnicity not reported Clear Response	☐ Caucasian, %: ☐ Caucasian, N: ☐ African American, %: ☐ African American, N: ☐ Asian or Asian American, %: ☐ Asian or Asian American, N: ☐ Hispanic or Latino, % ☐ Hispanic or Latino, N ☐ Other race/ethnicity, %: ☐ Other race/ethnicity, N:	☐ Caucasian, %: ☐ Caucasian, N: ☐ African American, %: ☐ African American, N: ☐ Asian or Asian American, %: ☐ Asian or Asian American, N: ☐ Hispanic or Latino, % ☐ Hispanic or Latino, N ☐ Other race/ethnicity, %: ☐ Other race/ethnicity, N:	☐ Caucasian, %: ☐ Caucasian, N: ☐ African American, %: ☐ African American, N: ☐ Asian or Asian American, %: ☐ Asian or Asian American, N: ☐ Hispanic or Latino, % ☐ Hispanic or Latino, N ☐ Other race/ethnicity, %: ☐ Other race/ethnicity, N:
Weight/BMI (weight units are preferred) ○ Weight/BMI not reported Clear Response	☐ Mean weight (include units): ☐ Median weight (include units): ☐ Mean BMI (kg/m2): ☐ Median BMI (kg/m2): ☐ Other, only weight/BMI categories reported	☐ Mean weight (include units): ☐ Median weight (include units): ☐ Mean BMI (kg/m2): ☐ Median BMI (kg/m2): ☐ Other, only weight/BMI categories reported	☐ Mean weight (include units): ☐ Median weight (include units): ☐ Mean BMI (kg/m2): ☐ Median BMI (kg/m2): ☐ Other, only weight/BMI categc
Baseline HbA1c ○ % ○ mmol/mol ○ mmol/L ○ HbA1c not reported Clear Response	☐ Mean HbA1c: ☐ Median HbA1c:	☐ Mean HbA1c: ☐ Median HbA1c:	☐ Mean HbA1c: ☐ Median HbA1c:
Duration of diabetes ○ Days ○ Weeks ○ Months ○ Years ○ Duration of diabetes not reported Clear Response	☐ Mean: ☐ Median:	☐ Mean: ☐ Median:	☐ Mean: ☐ Median:
Number of withdrawals and/or losses to followup ○ Withdrawals/loss to followup not reported ○ Not applicable (i.e., time to event analysis) Clear Response	☐ %: ☐ N:	☐ %: ☐ N:	☐ %: ☐ N:

Comments (limit 250 characters)

Comments (limit 250 characters)

Comments (limit 250 characters)

76. Results only reported by subgroup

○ Subgroup (specify):
Clear Response

Submit Form and go to or Skip to Next

Outcomes Form, KQ1–KQ3

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Diabetes Medications Outcomes Form

Fill out this form for all included studies*
Outcome of interest being reported on this form (check only one outcome under KQ1, KQ2, or KQ3 on this form):

Key Question 1 (Intermediate outcomes)

Outcome	Units
Key Question 1 (Intermediate outcomes) ○ HbA1c (Do NOT abstract for Met vs. SU comparison) ○ Weight (Do NOT abstract for Met vs. SU or MET vs. TZD) ○ BMI (ONLY if weight is not reported) ○ Systolic blood pressure (ONLY FOR SGLT-2 or GLP-1 comparisons) ○ Heart rate (ONLY FOR SGLT-2 or GLP-1 comparisons) Clear Response	Indicate units ○ % ○ mmol/mol ○ mmol/L ○ kg ○ lb ○ kg/m2 ○ mmHg ○ BPM Clear Response

Key Question 2 (Long-term outcomes)

Outcome	Definition
Key Question 2 (Long-term outcomes) ○ All-cause mortality ○ Cardiovascular mortality ○ Cardiovascular morbidity (e.g., myocardial infarction, acute coronary syndrome, arrhythmia, cardiac procedures, like percutaneous coronary intervention) ○ Cerebrovascular mortality/disease (e.g., stroke, TIA) ○ Incident diabetic retinopathy (macular edema will be captured under Key Question 3) ○ Incident diabetic nephropathy (e.g., mean eGFR, urinary albumin:creatinine ratio, changes in proteinuria or microalbuminuria, ESRD, dialysis outcomes, etc) ○ Incident diabetic neuropathy Clear Response	

Key Question 3 (Adverse event or side effect – Do NOT abstract for Met vs SU comparisons except cancer outcomes)

Outcome	Definition
Key Question 3 (Adverse event or side effect) ○ Hypoglycemia - mild/moderate ○ Hypoglycemia - severe/major ○ Hypoglycemia - total (only if not separated by mild/moderate/severe) ○ Liver failure ○ Congestive heart failure ○ Lactic acidosis ○ Cancer ○ Severe allergic reaction (including hypersensitivity reaction) ○ Hip fracture (for SGLT-2 inhibitor comparisons only) ○ Non-hip fracture (for SGLT-2 inhibitor comparisons only) ○ Pancreatitis ○ Volume depletion (for SGLT-2 inhibitor comparisons only) ○ Macular edema ○ Decreased vision ○ Gastrointestinal side effects (nausea, vomiting, diarrhea, dyspepsia, abdominal pain, total) ○ Impaired renal function (for SGLT-2 inhibitor comparisons only; same outcomes as nephropathy) ○ Genital or mycotic infection ((e.g., sexually transmitted disease or yeast or Bacterial vaginosis) ○ Urinary tract infections (for SGLT-2 inhibitors only) ○ Other serious adverse event (e.g., nocturnal hypoglycemia, osmotic diuresis) Clear Response	Defined as... ○ Specify: ○ Unspecified Clear Response

If applies to Key Question 3 (adverse events and/or safety outcomes), please answer questions 12.

12. Was the mode of adverse event collection active or passive?
If administrative database study, select passive.

○ Active (Active ascertainment of harms indicates (a) that participants are asked about the occurrence of specific harms in structured questionnaires or interviews or pre-defined laboratory or diagnostic tests, usually performed at pre-specified time intervals and/or (b) that the potential occurrence of harmful events are collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery. These events are potentially expected harms as a result of the intervention.)
○ Passive (Passive ascertainment of harms occurs when study participants spontaneously report (on their own initiative) or are allowed to report harmful events not probed with active ascertainment. In some studies, laboratory or diagnostic tests are only ordered if a particular event is suspected. For example, a study participant is suspected of having a stroke based on clinical presentation; the authors would indicate that brain imaging tests would then be ordered to confirm the presence or absence of the stroke.)
○ Not reported/unclear
Clear Response

ANSWER FOR ALL OUTCOMES:

13. Were results available for an "intention-to-treat" analysis (i.e., not per-protocol or "on treatment" analysis) for this outcome?

- ○ Yes
- ○ No
- ○ Not reported
- ○ Not applicable (e.g., cohort)

Clear Response

14. What is the followup time for this outcome? **(Only report the longest followup time.)**	Specify units:
○ (specify): ☐ ○ Not reported Clear Response	Select an Answer

Continuous outcomes (Most of outcomes for Key Question 1)

Table I. Mean difference from other intervention group measures of outcome (between-group difference). When filling out this table, please note that the point estimate should reflect this formula: (Final - Baseline for the intervention group) - (Final - Baseline for the reference group). You do not need to calculate this.

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign)	Measure of variability	95% CI or IQR	p-value (Record exact p-value)	Indicate reference group
		○ Mean ○ Median ○ Other (specify): ☐ ○ Not reported Clear Response	○ SE ○ SD ○ Other (specify): ☐ ○ Not reported Clear Response	○ 95% CI ○ IQR ○ Not reported Clear Response	○ Not reported Clear Response	
Main Intervention	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐	Select an Answer
Comparison A	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐	Select an Answer
Comparison B	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐	Select an Answer
Comparison C	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐	Select an Answer
Comparison D	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐	Select an Answer
Comparison E	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐	Select an Answer

Table II. Mean difference from baseline to final measures of outcome (within-group difference)
(This should be Final - Baseline. If values decrease, be sure to indicate with a negative sign (-)).

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign)	Measure of variability	95% CI or IQR	p-value (Record exact p-value)
		○ Mean ○ Median ○ Other (specify): ☐ ○ Not reported Clear Response	○ SE ○ SD ○ Other (specify): ☐ ○ Not reported Clear Response	○ 95% CI ○ IQR ○ Not reported Clear Response	○ Not reported Clear Response
Main Intervention	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐
Comparison A	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐
Comparison B	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐
Comparison C	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐
Comparison D	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐
Comparison E	○ N for analysis ☐ ○ Baseline N ☐ Clear Response	☐	☐	☐ Lower limit ☐ ☐ Upper limit ☐	☐

Table III. Baseline measures of cohort

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign) ○ Mean ○ Median ○ Other (specify): ○ Not reported Clear Response	Measure of variability ○ SE ○ SD ○ Other (specify): ○ Not reported Clear Response	95% CI or IQR ○ 95% CI ○ IQR ○ Not reported Clear Response	p-value (Record exact p-value) ○ Not reported Clear Response	Indicate reference group
Main Intervention	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer
Comparison A	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer
Comparison B	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer
Comparison C	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer
Comparison D	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer
Comparison E	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer

Table IV. Final measures of outcome

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign) ○ Mean ○ Median ○ Other (specify): ○ Not reported Clear Response	Measure of variability ○ SE ○ SD ○ Other (specify): ○ Not reported Clear Response	95% CI or IQR ○ 95% CI ○ IQR ○ Not reported Clear Response	p-value (Record exact p-value) ○ Not reported Clear Response	Indicate reference group
Main Intervention	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer
Comparison A	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer
Comparison B	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer
Comparison C	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer
Comparison D	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer
Comparison E	○ N for analysis ○ Baseline N Clear Response			☐ Lower limit ☐ Upper limit		Select an Answer

Dichotomous Outcomes (Most of outcomes for Key Questions 2 and 3)

Table V. Incidence of the outcome by intervention group

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Outcome measure/numerator	Denominator	p-value (Record exact p-value)	Indicate reference group
		Not reported Clear Response	Select an Answer	Not reported Clear Response	
Main intervention	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer
Comparison A	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer
Comparison B	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer
Comparison C	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer
Comparison D	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer
Comparison E	N for analysis Baseline N Clear Response	# of patients with one or more events % of patients with one or more events # of events			Select an Answer

Table VI. Measures of association for comparison of outcome between intervention groups

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate	Measure of variability	95% Confidence interval	p-value (Record exact p-value)	Indicate reference group
		Relative risk Relative hazard Odds ratio Risk difference Other: Not reported Clear Response	SE SD Not reported Clear Response	Not reported Clear Response	Not reported Clear Response	
Main intervention	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison A	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison B	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison C	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison D	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer
Comparison E	N for analysis Baseline N Clear Response			Lower limit Upper limit		Select an Answer

What were the results adjusted for in the final model?

- [ ] Results are not adjusted
- [ ] Age
- [ ] Sex
- [ ] Race/SES
- [ ] BMI or weight
- [ ] Glycemic control
- [ ] Comorbidities
- [ ] Duration of diabetes
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):

244. Comments **(limit 250 characters)**

245. Comments **(limit 250 characters)**

246. Comments **(limit 250 characters)**

247. Results reported for subgroup

- ( ) Subgroup (specify)

Clear Response

Submit Form and go to or Skip to Next

Study Quality Form for Randomized Controlled Trials

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Diabetes Medications
Quality Form for Trials

Complete this form only for randomized controlled trials.

1. Was the study described as **randomized** (this includes the use of words such as randomly, random and randomization)?

Yes No Not reported Clear Response

3. Was the study described as **double blind**?

Yes No Not reported/Can't tell Clear Response

5. Was there a description of **withdrawals and dropouts**?

Yes: the number and the reasons for withdrawals in each group was stated or it was stated that there were no withdrawals
(if subjects were not included in the analysis, they must state the number and reasons for not including them in the analysis)

No Clear Response

6. Comments **(limit 250 characters)**

7. Comments **(limit 250 characters)**

8. Comments **(limit 250 characters)**

Submit Form and go to or Skip to Next

Study Quality Form for Nonrandomized Study

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Diabetes Medications
Downs and Black Checklist for Measuring Study Quality

Complete this form only for non-randomized studies.

REPORTING

1. Is the **hypothesis/aim/objective** of the study clearly described?

   ○ Yes ○ No Clear Response

2. Are the **main outcomes** to be measured clearly described in the **Introduction or Methods section**?
   If the main outcomes are first mentioned in the Results section, the question should be answered 'no.'

   ○ Yes ○ No Clear Response

3. Are the **characteristics of the subjects** included in the study clearly described?
   In trials, inclusion and/or exclusion criteria should be given.

   ○ Yes ○ No Clear Response

4. Are the **interventions of interest** clearly described?
   Treatment and placebo (where relevant) that are to be compared should be clearly described

   ○ Yes ○ No Clear Response

5. Are the **distributions of principal confounders** in each group of subjects to be compared clearly described?
   A list of principal confounders is provided.

   ○ Yes ○ No Clear Response

6. Are the **main findings** of the study clearly described?
   Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does NOT cover statistical tests which are considered below).

   ○ Yes ○ No Clear Response

7. Does the study provide estimates of the **random variability** in the data for the main outcomes?
   In non-normally distributed data the inter-quartile range of results should be reported.
   In normally distributed data the standard error, standard deviation or confidence intervals should be reported.
   If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes.'

   ○ Yes ○ No Clear Response

8. Have all important **adverse events** tht may be a consequence of the intervention been reported?
   This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events.
   If administrative database, select "Not applicable."

   ○ Yes ○ No ○ Not applicable Clear Response

9. Have the characteristics of **subjects lost to follow-up** been described?
   This should be answered 'yes' where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion.
   This should be answered 'no' where a study does not report the number of patients lost to follow-up.

   ○ Yes ○ No Clear Response

10. Have **actual probability values** been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

    ○ Yes ○ No Clear Response

EXTERNAL VALIDITY

11. Were the **subjects asked to participate in the study representative** of the entire population from which they were recruited?
    The study must identify the source population for patients and describe how the patients were selected.
    Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered 'unable to determine.'
    If administrative database study, select "Not applicable."

    ○ Yes ○ No ○ Unable to determine ○ Not applicable Clear Response

12. Were those **subjects who were prepared to participate representative** of the entire population from which they were recruited?
    The proportion of those asked who agreed should be stated.
    Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.
    If administrative database study, select "Not applicable."

    ○ Yes ○ No ○ Unable to determine ○ Not applicable Clear Response

13. Were the **staff, places, and facilities** where the subjects were treated/tested **representative** of the testing the majority of subjects receive?
    For the question to be answered 'yes' the study should demonstrate that the testing was representative of that in use in the source population. The question should be answered 'no' if, for example, the testing was undertaken in a specialist center unrepresentative of the hospitals most of the source population would attend.

    ○ Yes ○ No ○ Unable to determine Clear Response

INTERNAL VALIDITY - BIAS

14. Was an attempt made to **blind study subjects** to the intervention they have received?
    For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

    ○ Yes ○ No Clear Response

15. Was an attempt made to **blind those measuring the main outcomes** of the intervention?

    ○ Yes ○ No ○ Unable to determine ○ Not feasible Clear Response

16. If any of the results of the study were based on **"data dredging"**, was this made clear?
Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer 'yes.'

◯ Yes ◯ No ◯ Unable to determine Clear Response

17. In **trials and cohort studies**, do the analyses **adjust for different lengths** of follow-up of patients?
Where follow-up was the same for all study participants the answer should be 'yes.' If different lengths of follow-up were adjusted, for example, by survival analysis, the answer should be 'yes.'
Studies where differences in follow-up are ignored should be answered 'no.'

◯ Yes ◯ No ◯ Unable to determine ◯ Not applicable (i.e. no followup for this type of study) Clear Response

18. Were the **statistical tests** used to assess the main outcomes appropriate?
The statistical techniques used must be appropriate to the data. For example nonparametric
methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered 'yes.' If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered 'yes.'

◯ Yes ◯ No ◯ Unable to determine Clear Response

19. Was **compliance** with the interventions reliable?
Where there was non compliance with the allocated treatment or where htere was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.
For administrative database studies:
• If they assessed adherence/compliance (such as using the medication possession ratio or days supply in-hand) and adherence/compliance
was 80% or greater, enter Yes
was less than 80%, enter No
was not reported, enter Unable to Determine
• If patients were censored/changed to different medication group when switched medications, enter Yes
• If the exposure period (i.e., examined medication use in 180 days prior to event) was shorter than 6 months, enter Yes
• If they required a minimum duration of medication use (such as 180 days) and the duration of follow up was short (such as 1 year), enter Yes (However, if they required a minimum duration of medication use (such as 180 days) and the duration of follow up was long (such as 5 years), enter Unable to Determine)
• If pts were assigned to a treatment group based on initial/baseline prescription only without mention of follow up assessment, enter Unable to Determine
• If the participants were allowed to change medications but were analyzed according to baseline medication, enter Unable to Determine (However, if baseline and censored medication analyses were done and yielded similar magnitude of effect/statistical significance results, enter Yes)

◯ Yes ◯ No ◯ Unable to determine Clear Response

20. Were the **main outcome measures** used accurate (valid and reliable)?
For studies where the outcome measures are clearly described, the question should be answered 'yes.' For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered 'yes.'
For administrative database studies:
• If all outcomes came from state/national cancer registry or death master file, enter Yes
• If all outcomes confirmed by chart review, enter Yes
• If a subset of outcomes were chart reviewed and performance statistics (i.e., sensitivity/specificity) provided for their validity, enter Yes
• If outcomes were identified by ICD-9-CM or ICD-10-CM and a citation is provided based on this exact cohort that the codes used have been confirmed with a chart review, enter Yes
• If outcomes were identified by ICD-9-CM or ICD-10-CM and a different cohort is cited OR no citation of validity is provided, enter Unable to Determine
• If some outcomes meet the definition of Yes and others meet the definition for Unable to Determine, enter Unable to Determine

◯ Yes ◯ No ◯ Unable to determine Clear Response

INTERNAL VALIDITY - CONFOUNDING AND SELECTION BIAS

21. Were the subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) **recruited from the same population**?
For example, subjects for all comparison groups should be selected from the same school. The question should be answered unable to determine for cohort where there is no information concerning the source of subjects included in the study.

◯ Yes ◯ No ◯ Unable to determine Clear Response

22. Were study subjects in different testing groups (trials and cohort studies) or were the cases and controls (case-control studies) **recruited over the same period of time**?
For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

◯ Yes ◯ No ◯ Unable to determine Clear Response

23. Were study subjects **randomized** to intervention groups?
Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example, alternate allocation would score no because it is predictable.

◯ Yes ◯ No ◯ Unable to determine Clear Response

24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
All non-randomized studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

◯ Yes ◯ No ◯ Unable to determine Clear Response

25. Was there **adequate adjustment for confounding** in the analyses from which the main findings were drawn?
This question should be answered 'no' for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses.
In non-randomized studies, if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered 'no.'
"Yes" for adjusted for all major confounders (demographic and common comorbidities) and "Yes, some" if some, not all major confounders were adjusted for.

◯ Yes (adjusted for all confounders) ◯ Yes, some (adjusted for some confounders) ◯ No (did not adjust for confounders) ◯ Unable to determine
◯ Not applicable (i.e. diagnostic test paper) Clear Response

26. Were **losses of subjects to follow-up** taken into account?
If the numbers of subjects lost to follow-up are not reported, the question should be answered 'unable to determine.' If the proportion lost to follow-up was too small to affect the main findings, the question should be answered 'yes.'

◯ Yes ◯ No ◯ Unable to determine ◯ Not applicable (i.e. no followup period such as KQ1) Clear Response

POWER

27. Did they report a power calculation?

◯ Yes ◯ No Clear Response

28. Comments (limit 250 characters)

29. Comments (limit 250 characters)

30. Comments (limit 250 characters)

Submit Form and go to ⇕ or Skip to Next

Appendix C. List of Excluded Studies

. Insulin vs. Sulfonylureas as add-on to metformin. Drug and Therapeutics Bulletin. 2014;52(10):112-3.
Meeting abstract

. Risk of acute pancreatitis with 'gliptins'. Drug Ther Bull. 2012;50(12):134.
No original data

.A therapeutic option for the management of type 2 diabetes. 2013.
No original data

. Correction To Comparison Of Empaglifl Ozin And Glimepiride As Add-On To Metformin In Patients With Type 2 Diabetes: A 104-Week Randomised, Active-Controlled, Double-Blind, Phase 3 Trial Lancet Diabetes Endocrinol 2014; 2: 691-700. The Lancet Diabetes and Endocrinology. 2015;3(3):e2.
Erratum; No original data

. ERRATUM: Valentine V, Hinnen D. Clinical Implications of Canagliflozin Treatment in Patients With Type 2 Diabetes. Clinical Diabetes 2014;33: 5-13 (DOI: 10.2337/diaclin.33.2.96). Clin Diabetes. 2015 Apr;33(2):96. PMID: 25896636.
No original data

Aaboe K, Knop FK, Vilsboll T, et al. Twelve weeks treatment with the DPP-4 inhibitor sitagliptin improves glycaemic control, but does not improve GLP-1 secretion, in patients with type 2 diabetes - A randomised trial. Diabetologia. 2009;52(S1):S294.
No original data

Aaboe K, Knop FK, Vilsboll T, et al. Twelve weeks treatment with the DPP-4 inhibitor, Sitagliptin, Reduces total PYY and PYY3-36 and increases PYY1-36 but has no effect on intact GLP-2 in subjects with type 2 diabetes Mellitus-A randomized trial. Diabetes. 2009;58((Aaboe K.; Knop F.K.; Vilsboll T.; Deacon C.F.; Holst J.J.; Madsbad S.; Krarup T.)).
Meeting abstract

Aaboe K, Vilsboll T, Knop FK, et al. Twelve weeks treatment with the DPP-4 Inhibitor, Sitagliptin, Improves the Insulin-Secreting capacity of the P-Cells in subjects with type 2 diabetes Mellitus-A randomized trial. Diabetes. 2009;58((Aaboe K.; Vilsboll T.; Knop F.K.; Deacon C.F.; Holst J.J.; Madsbad S.; Krarup T.)).
Meeting abstract

Abbatecola AM, Lattanzio F, Molinari AM, et al. Rosiglitazone and cognitive stability in older individuals with type 2 diabetes and mild cognitive impairment. Diabetes Care. 2010 Aug;33(8):1706-11. PMID: 20435794.
No outcome of interest; Does not meet study design criteria

Abbatecola AM, Paolisso G. Rosiglitazone and cognitive stability in older persons with type 2 diabetes and mild cognitive impairment. Diabetologia. 2009;52(S1):S67.
Meeting abstract

Abdulkadir AA, Thanoon IA. Comparative Effects of Glibenclamide and Metformin on C-Reactive Protein and Oxidant/Antioxidant Status in Patients with Type II Diabetes Mellitus. Sultan Qaboos Univ Med J. 2012 Feb;12(1):55-61. PMID: 22375259.
Followup less than 3 months

Abe M, Okada K, Maruyama T, et al. Clinical effectiveness and safety evaluation of long-term pioglitazone treatment for erythropoietin responsiveness and insulin resistance in type 2 diabetic patients on

hemodialysis. Expert Opin Pharmacother. 2010 Jul;11(10):1611-20. PMID: 20540652.
Background medications

Adetunji O, Skrivanek Z, Tahbaz A, et al. A post-hoc pooled analysis of two placebo controlled phase 3 trials, Assessment of Weekly AdministRation of LY2189265 in Diabetes-1 and-5 (AWARD-1 and AWARD-5): Dulaglutide compared with exenatide, sitagliptin, and placebo. Diabetologie und Stoffwechsel. 2014;9((Adetunji O.; Tahbaz A.) Eli Lilly and Company, Medical Affairs, Basingstoke, United Kingdom).
Meeting abstract

Adetunji O, Skrivanek Z, Tahbaz A, et al. A posthoc pooled analysis of two placebo-controlled phase 3 trials, Assessment of Weekly Administration of LY2189265 in Diabetes 1 and 5 (AWARD-1 and AWARD-5): Dulaglutide compared with exenatide, sitagliptin and placebo. Diabetic Medicine. 2014;31((Adetunji O.; Tahbaz A.) Medical Department, Eli Lilly and Company, Basingstoke, United Kingdom):50-1.
Meeting abstract

Agarwala A, Givens E, McGuire DK, et al. Rosiglitazone increases cholesterol efflux capacity in patients with type 2 diabetes. Journal of Investigative Medicine. 2014;62(2):510-1.
Meeting abstract

Agrawal A, Pradeep. To study the pattern of use and efficacy of anti-diabetic drugs in controlling adequate glycemic levels in diabetic patients in Navi Mumbai. Australasian Medical Journal. 2012;5(1):88-9.
Meeting abstract

Ajdi F, Khabbal Y, Safi S. ADR of oral antidiabetic. Drug Safety. 2009;32(10):949-50.
Meeting abstract

Al Sifri S, Basiounny A, Echtay A, et al. The incidence of hypoglycaemia in Muslim patients with type 2 diabetes treated with sitagliptin or a sulphonylurea during Ramadan: a randomised trial. Int J Clin Pract. 2011 Nov;65(11):1132-40. PMID: 21951832.
No drug comparison of interest

Alba M, Ahren B, Inzucchi SE, et al. Initial combination therapy with sitagliptin and pioglitazone: Complementary effects on postprandial glucose and islet cell function. Canadian Journal of Diabetes. 2009;33(3):319-20.
Meeting abstract

Alexanderson-Rosas E, de Jesus Martinez A, Ochoa-Lopez JM, et al. [Effects of the combined treatment with Metformin/Glimepiride on endothelial function of patients with type 2 diabetes mellitus. A positron emission tomography (PET) evaluation study]. Arch Cardiol Mex. 2009 Oct-Dec;79(4):249-56. PMID: 20191984.
Follow-up less than three months

Alkharfy KM, Al-Daghri NM, Sabico SB, et al. Vitamin D supplementation in patients with diabetes mellitus type 2 on different therapeutic regimens: a one-year prospective study. Cardiovasc Diabetol. 2013 Aug 7;12(1):113. PMID: 23924389.
No drug comparison of interest

Allen E, Berglind N. Saxagliptin vs glipizide as add-on therapy to metformin in patients with type 2 diabetes: A 2-year assessment of HbA1c, hypoglycaemia, and weight gain in a randomised, double-blind study.

Diabetologia. 2011;54((Allen E.; Berglind N.) Bristol-Myers Squibb, Princeton, United States):S337.
Meeting abstract

Allen E, Donovan M, Berglind N, et al. Efficacy of saxagliptin according to patient baseline characteristics: A pooled analysis of three add-on pivotal randomised phase 3 clinical trials. Diabetologia. 2010;53((Allen E.; Donovan M.; Berglind N.) Bristol-Myers Squibb, Princeton, United States):S328.
Meeting abstract

Allen E, Karyekar C, Ohman P. Safety profile of saxagliptin (SAXA) in combination with 2 other agents: Data from dual-therapy trials in patients receiving rescue treatment. Diabetes. 2011;60((Allen E.; Karyekar C.; Ohman P.) Princeton, United States):A619-A20.
Meeting abstract

Allen E, Slater J, Bryzinski B, et al. Efficacy and safety of saxagliptin (SAXA) in patients with type 2 diabetes stratified by cardiovascular risk factors. Diabetologia. 2012;55((Allen E.; Slater J.) Medical Affairs, Bristol-Myers Squibb, Princeton, United States):S346-S7.
Meeting abstract

Alvarez-Guisasola F, Yin DD, Nocea G, et al. Association of hypoglycemic symptoms with patients' rating of their health-related quality of life state: a cross sectional study. Health Qual Life Outcomes. 2010;8:86. PMID: 20723229.
Does not apply; No drug comparison of interest

Ambrosius WT, Danis RP, Goff DC, Jr., et al. Lack of association between thiazolidinediones and macular edema in type 2 diabetes: the ACCORD eye substudy. Arch Ophthalmol. 2010 Mar;128(3):312-8. PMID: 20212201.
Background medications

Ametov AS, Gusenbekova DG. [Effect of dipeptidyl peptidase-4 inhibitors on lipid metabolism in patients with type 2 diabetes mellitus]. Ter Arkh. 2014;86(8):85-9. PMID: 25306750.
Non-English Language

Araki A, Iimuro S, Sakurai T, et al. Long-term multiple risk factor interventions in Japanese elderly diabetic patients: The Japanese Elderly Diabetes Intervention Trial - study design, baseline characteristics and effects of intervention. Geriatrics and Gerontology International. 2012;12(SUPPL.1):7-17.
Does not apply

Aravind SR, Ismail SB, Balamurugan R, et al. Hypoglycemia in patients with type 2 diabetes from India and Malaysia treated with sitagliptin or a sulfonylurea during Ramadan: a randomized, pragmatic study. Curr Med Res Opin. 2012 Aug;28(8):1289-96. PMID: 22738801.
Follow-up less than three months; Background medications

Arcidiacono B, Capula C, Chiefari E, et al. Glycemic efficacy of liraglutide is linked to gender in italian type 2 diabetic patients. Diabetes. 2014;63((Arcidiacono B.; Capula C.; Chiefari E.; Vero A.; Oliverio R.; Puccio L.; Liguori R.; Pullano V.; Tirinato D.; Foti D.; Vero R.; Brunetti A.) Catanzaro, Italy, Soverato, Italy):A288.
Meeting abstract

Ardawi MS, Akbar D, Al-Shaik A, et al. Circulating sclerostin, bone turnover markers and BMD in type-2 diabetic women treated with metformin or pioglitazone. Journal of Bone and Mineral Research.

2013;28((Ardawi M.-S.; Rouzi A.) Center of Excellence for Osteoporosis Research, Faculty of Medicine, Saudi Arabia).
Meeting abstract

Ardawi MS, Akbar D, Alshaikh A, et al. Circulating sclerostin, bone turnover markers and BMD in type 2 diabetic women treated with metformin or pioglitazone. Osteoporosis International. 2013;24(1):S132-S3.
Meeting abstract

Arjona Ferreira JC, Corry D, Mogensen CE, et al. Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. Am J Kidney Dis. 2013 Apr;61(4):579-87. PMID: 23352379.
Comorbidity

Arjona Ferreira JC, Corry D, Mogensen CE, et al. Efficacy and safety of sitagliptin vs. glipizide in patients with type 2 diabetes mellitus and end-stage renal disease on dialysis: A 54-week randomised trial. Diabetes, Stoffwechsel und Herz. 2011;20(6):430.
Meeting abstract

Arjona Ferreira JC, Marre M, Rabelink TJ, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate to severe chronic renal insufficiency. Diabetes, Stoffwechsel und Herz. 2011;20(6):419.
Meeting abstract

Armstrong M, Falahati A, Houlihan DD, et al. Effects of two years of liraglutide treatment on fatty liver disease in patients with type 2 diabetes: Analysis of the liraglutide effect and action in diabetes-2 extension trial. Gut. 2010;59((Armstrong M.; Falahati A.; Elbrand B.; Schmidt W.E.; Gough S.; Newsome P.N.) Centre for Liver Research, University of Birmingham, United Kingdom):A1-A2.
Meeting abstract

Armstrong M, Houlihan D, Schmidt W, et al. Effects of once-daily liraglutide on fatty liver disease in patients with type 2 diabetes (T2D) after 2 years' treatment: Retrospective-analysis of the lead-2 extension trial. Journal of Diabetes. 2011;3((Armstrong M.; Houlihan D.; Newsome P.) Centre for Liver Research, University of Birmingham, Birmingham, United Kingdom):11.
Meeting abstract

Armstrong MJ, Falahati A, Houlihan D, et al. Effects of two years of liraglutide treatment on fatty liver disease in patients with type 2 diabetes: Analysis of the lead-2 extension trial. Hepatology. 2010;52((Armstrong M.J.; Houlihan D.; Newsome P.N.) Centre for Liver Research, University of Birmingham, Birmingham, United Kingdom):620A.
Meeting abstract

Armstrong MJ, Houlihan DD, Rowe IA, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. Aliment Pharmacol Ther. 2013 Jan;37(2):234-42. PMID: 23163663.
Handsearch

Armstrong MJ, Houlihan DD, Rowe IA, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes with elevated liver enzymes: Individual patient data meta-analysis of the LEAD programme. The Lancet. 2013;381((Armstrong M.J., mattyarm2010@googlemail.com; Houlihan D.D.; Rowe I.A.; Tomlinson J.W.) Centre for Liver Research, Institute of Biomedical Research, University of Birmingham,

Edgbaston, Birmingham, United Kingdom):S20.
Meeting abstract

Arnolds S, Sawicki PT. Liraglutide and the preservation of pancreatic (beta)-cell function in early type 2 diabetes: The libra trial. Diabetes care 2014;37:3270-3278. Diabetes Care. 2015;38(2):e25.
Meeting abstract

Arulanandham A, Raju A, Pradeep Rajkumar LA, et al. Prevalence of clinically significant macular edema [CSME] among glitazone users and non- users of type-2 DM patients with diabetic retinopathy. International Journal of Drug Development and Research. 2012;4(2):132-7.
No drug comparison of interest

Asanuma H, Kitakaze M. [Prospective pioglitazone clinical trial in macrovascular events]. Nihon Rinsho. 2012 May;70 Suppl 3:301-8. PMID: 22768537.
No original data; No drug comparison of interest

Aschner P, Sethi B, Gomez-Peralta F, et al. Glargine vs. premixed insulin for management of type 2 diabetes patients failing oral antidiabetic drugs: The GALAPAGOS study. Diabetes. 2013;62((Aschner P.; Sethi B.; Gomez-Peralta F.; Landgraf W.; Dain M.-P.; Pilorget V.; Comlekci A.) Bogota, Colombia, Hyderabad, India, Segovia, Spain, Frankfurt, Germany, Paris, France, Izmir, Turkey):A241-A2.
Meeting abstract

Aschner P, Sethi B, Gomez-Peralta F, et al. Insulin glargine compared with premixed insulin for management of insulin-naive type 2 diabetes patients uncontrolled on oral antidiabetic drugs: the open-label, randomized GALAPAGOS study. J Diabetes Complications. 2015 Aug;29(6):838-45. PMID: 25981123.
Background medications

Aso Y, Takebayashi K, Inukai T, et al. Pioglitazone and cardiovascular events in type 2 diabetes: Effects of pioglitazone on cardiovascular outcomes in Japanese patients with type 2 diabetes in higashi-saitama (EPOCH Trial). Diabetes. 2011;60((Aso Y.; Takebayashi K.; Inukai T.; Katsumori K.; Owada K.; Nakamura T.; Naito T.; Itabashi H.; Morita K.; Sekine M.; Takahashi K.; Miyano H.; Takai T.) Koshigaya, Japan):A557.
Meeting abstract

Atchison L, Steinke EL. Relationship between social and economic factors in diabetes medication-prescribing patterns. Journal of the American Pharmacists Association. 2011;51(2):228.
Meeting abstract

Aubert RE, Herrera V, Chen W, et al. Rosiglitazone and pioglitazone increase fracture risk in women and men with type 2 diabetes. Diabetes Obes Metab. 2010 Aug;12(8):716-21. PMID: 20590749.
Aydin Y, Erden M, Ermis F, et al. Oral antidiabetics and insulins do not increase cancer risk. Acta Medica Mediterranea. 2013;29(4):859-67.
Background medications

Azar S, El-Mollayess GM, Al Shaar L, et al. Impact of thiazolidinediones on macular thickness and volume in diabetic eyes. Can J Ophthalmol. 2013 Aug;48(4):312-6. PMID: 23931472.
No drug comparison of interest; Does not account for confounding

Azar ST, Malha LP, Zantout MS, et al. Management and control of patients with type 2 diabetes mellitus in Lebanon: results

from the International Diabetes Management Practices Study (IDMPS). J Med Liban. 2013 Jul-Sep;61(3):127-31. PMID: 24422361.
Background medications

Azoulay L, Dell'Aniello S, Gagnon B, et al. Metformin and the incidence of prostate cancer in patients with type 2 diabetes. Cancer Epidemiol Biomarkers Prev. 2011 Feb;20(2):337-44. PMID: 21148757.
No drug comparison of interest

Azoulay L, Schneider-Lindner V, Dell'aniello S, et al. Combination therapy with sulfonylureas and metformin and the prevention of death in type 2 diabetes: a nested case-control study. Pharmacoepidemiol Drug Saf. 2010 Apr;19(4):335-42. PMID: 20052677.
Background medications

Azoulay L, Schneider-Lindner V, Dell'aniello S, et al. Thiazolidinediones and the risk of incident strokes in patients with type 2 diabetes: a nested case-control study. Pharmacoepidemiol Drug Saf. 2010 Apr;19(4):343-50. PMID: 19998318.
No drug comparison of interest

Azoulay L, Yin H, Filion KB, et al. The use of pioglitazone and the risk of bladder cancer in patients with type 2 diabetes. Pharmacoepidemiology and Drug Safety. 2012;21((Azoulay L.; Yin H.; Filion K.B.; Assayag J.; Suissa S.) Centre for Clinical Epidemiolog, Jewish General Hospital, Montreal, Canada):271.
Meeting abstract

Azoulay L, Yin H, Filion KB, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. BMJ. 2012;344:e3645. PMID: 22653981
Does not account for confounding

Bach RG, Brooks MM, Lombardero M, et al. Rosiglitazone and outcomes for patients with diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Circulation. 2013 Aug 20;128(8):785-94. PMID: 23857320.
No drug comparison of interest

Bailey CJ, Day C, Campbell IW, et al. Glycaemic control and cardiovascular outcome trials in type 2 diabetes. British Journal of Diabetes and Vascular Disease. 2012;12(4):161-4.
No original data

Bailey CJ, Gross JL, Bastone L, et al. Dapagliflozin as an add-on to metformin lowers hyperglycaemia in type 2 diabetes patients inadequately controlled with metformin alone. Diabetologia. 2009;52(S1):S76.
Meeting abstract

Bailey CJ, Gross JL, Hennicken D, et al. Correction to Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: A randomized, double-blind, placebo-controlled 102-week trial [BMC Medicine, 11, 193, (2013)]. BMC Med. 2013;11(1).
Meeting abstract

Bailey CJ, Gross JL, Yadav M, et al. Sustained efficacy of dapagliflozin when added to metformin in type 2 diabetes inadequately controlled by metformin monotherapy. Diabetologia. 2011;54((Bailey C.J.) Aston University, Birmingham, United Kingdom):S67.
Meeting abstract

Bailey CJ, Iqbal N, T'Joen C, et al. Dapagliflozin monotherapy in drug-naive patients with diabetes: a randomized-

controlled trial of low-dose range. Diabetes Obes Metab. 2012 Oct;14(10):951-9. PMID: 22776824.
No drug comparison of interest

Bailey CJ, Morales Villegas EC, Woo V, et al. Efficacy and safety of dapagliflozin monotherapy in people with Type 2 diabetes: a randomized double-blind placebo-controlled 102-week trial. Diabet Med. 2014 Nov 8PMID: 25381876.
No drug comparison of interest

Bailey CJ, Wilding J, Nauck MA, et al. Sustained reductions in weight and HbA1c with dapagliflozin: Long-term results from phase III clinical studies in type 2 diabetes. Diabetologia. 2012;55((Bailey C.J.) Aston University, School of Life and Health Sciences, Birmingham, United Kingdom):S295.
Meeting abstract

Bailey RA, Damaraju CV, Martin SC, et al. Attainment of diabetes-related quality measures with canagliflozin versus sitagliptin. Am J Manag Care. 2014 Jan;20(1 Suppl):s16-24. PMID: 24512193.
No drug comparison of interest

Bailey RA, Vijapurkar U, Martin S, et al. Composite quality measure (CQM) attainment in overweight/obese patients with type 2 diabetes mellitus treated with canagliflozin 300 mg (CANA) or sitagliptin 100 mg (SITA). Value in Health. 2014;17(3):A239.
Meeting abstract

Bailey RA, Vijapurkar U, Meininger GE, et al. Diabetes-related quality measure attainment: canagliflozin versus sitagliptin based on a pooled analysis of 2 clinical trials. Am J Manag Care. 2014 Dec;20(13 Suppl):s296-305. PMID: 25734218.
No drug comparison of interest

Bailey T, Pratley R, Buse J, et al. Liraglutide produces greater reductions in HbA1c levels compared with sitagliptin or exenatide across five baseline HbA1c categories. Diabetologia. 2011;54((Bailey T.) AMCR Institute, Escondido, United States):S321.
Meeting abstract

Bain SC, Skrivanek Z, Tahbaz A, et al. Efficacy of long-acting once weekly dulaglutide compared with short-acting twice daily (bid) exenatide in patients with Type 2 diabetes: A posthoc analysis to determine the influence of baseline HbA1c in the Assessment of Weekly Administration of LY2189265 in Diabetes-1 (AWARD-1) trial. Diabetic Medicine. 2014;31((Bain S.C.) Institute of Life Science, Swansea University, Abertawe Bro Morgannwg University Health Board, Swansea, United Kingdom):50.
Meeting abstract

Bain SC, Stella P, Cao A. Significantly reduced body mass index with liraglutide 1.2 mg treatment versus glimepiride may have an impact on cardiovascular risk in patients with type 2 diabetes. Diabetic Medicine. 2010;27(2):79.
Meeting abstract

Balena R, Wintle M, Meloni A, et al. Exenatide once weekly, glycaemic goals, and selected cardiovascular risk factors in patients with T2DM: A retrospective analysis of pooled clinical trial data. Diabetes, Stoffwechsel und Herz. 2011;20(6):430-1.
Meeting abstract

Bannister CA, Holden SE, Jenkins-Jones S, et al. Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched,

non-diabetic controls. Diabetes Obes Metab. 2014 Nov;16(11):1165-73. PMID: 25041462.
Does not account for confounding

Barnett A, Huisman H, Jones R, et al. Efficacy and safety of linagliptin in elderly patients ((greater-than or equal to) 70 years) with type 2 diabetes. Diabetes. 2012;61((Barnett A.; Huisman H.; Jones R.; Von Eynatten M.; Patel S.; Woerle H.-J.) Birmingham, United Kingdom):A260-A1.
Meeting abstract

Barnett AH, Charbonnel B, Donovan M, et al. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. Curr Med Res Opin. 2012 Apr;28(4):513-23. PMID: 22313154.
No drug comparison of interest

Barnett AH, Harper R, Toorawa R, et al. Linagliptin monotherapy improves glycaemic control in type 2 diabetes patients for whom metformin therapy is inappropriate. Diabetologia. 2010;53((Barnett A.H.) University of Birmingham, Heart of England NHS Foundation Trust, United Kingdom):S327.
Meeting abstract

Barnett AH, Mithal A, Manassie J, et al. A phase III trial of empagliflozin in patients with Type 2 diabetes with stage 2 or 3 chronic kidney disease (EMPA-REG RENAL(trademark)). Diabetic Medicine. 2014;31((Barnett A.H.) Diabetes Centre, Heart of England NHS Foundation Trust, University of Birmingham, Birmingham, United Kingdom):63.
Meeting abstract

Barnett AH, Mithal A, Manassie J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: A randomised, double-blind, placebo-controlled trial. The Lancet Diabetes and Endocrinology. 2014;2(5):369-84.
Background medications; No drug comparison of interest

Barnett AH, Mithal A, Manassie J, et al. Empagliflozin in patients with type 2 diabetes mellitus (T2DM) and renal impairment (RI). Diabetes. 2013;62((Barnett A.H.; Mithal A.; Manassie J.; Jones R.; Rattunde H.; Woerle H.J.; Broedl U.C.) Birmingham, United Kingdom, Delhi, India, Berkshire, United Kingdom, Ingelheim, Germany):A286.
Meeting abstract

Barnett AH, Tahrani AA, Von Eynatten M, et al. The novel DPP-4 inhibitor linagliptin is associated with a very low risk of hypoglycemia: Results from a large phase III program. Diabetes. 2011;60((Barnett A.H.; Tahrani A.A.; Von Eynatten M.; Emser A.; Patel S.; Woerle H.J.) Birmingham, United Kingdom):A623.
Meeting abstract

Barrington P, Chien JY, Showalter HDH, et al. A 5-week study of the pharmacokinetics and pharmacodynamics of LY2189265, a novel, long-acting glucagon-like peptide-1 analogue, in patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2011;13(5):426-33.
Background medications; No drug comparison of interest

Barthelemy M, Boullu Sanchis S, Moreau F, et al. Substitution of insulin by exenatide in bad controlled type 2 diabetic patients: efficacy and predictive factors. Minerva Endocrinol. 2014 Jul 8PMID: 25003223.

Does not apply; Does not meet study design criteria

Barzilai N, Guo H, Mahoney EM, et al. Efficacy and tolerability of sitagliptin monotherapy in elderly patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin. 2011 May;27(5):1049-58. PMID: 21428727.
Placebo-controlled trial

Baser O, Tangirala K, Wei W, et al. Real-world outcomes of initiating insulin glargine-based treatment versus premixed analog insulins among US patients with type 2 diabetes failing oral antidiabetic drugs. ClinicoEconomics and Outcomes Research. 2013;5(1):497-505.
No drug comparison of interest

Baser O, Wei W, Baser E, et al. Clinical and economic outcomes in patients with type 2 diabetes initiating insulin glargine disposable pen versus exenatide BID. J Med Econ. 2011;14(6):673-80. PMID: 21892858.
No drug comparison of interest; Background medications

Baser O, Wei W, Baser E. Clinical and economic outcomes in patients with type 2 diabetes initiating insulin glargine using disposable pen versus exenatide. Journal of Managed Care Pharmacy. 2011;17(3):237-8.
Meeting abstract

Basile J, Ptaszynska A, Ying L, et al. The effects of dapagliflozin on cardiovascular risk factors in patients with type 2 diabetes mellitus. Circulation: Cardiovascular Quality and Outcomes. 2012;5(3).
Meeting abstract

Bayraktar S, Hernadez-Aya LF, Lei X, et al. Effect of metformin on survival outcomes in diabetic patients with triple receptor-negative breast cancer. Cancer. 2012 Mar 1;118(5):1202-11. PMID: 21800293.
No drug comparison of interest

Bazelier M, Gallagher A, Vestergaard P, et al. Use of thiazolidinediones and risk of osteoporotic fracture: Disease or drugs? Osteoporosis International. 2012;23((Bazelier M.; Gallagher A.; De Vries F.) Utrecht University, Utrecht, Netherlands):S556.
Meeting abstract

Bazelier MT, Gallagher AM, van Staa TP, et al. Use of thiazolidinediones and risk of osteoporotic fracture: disease or drugs? Pharmacoepidemiol Drug Saf. 2012 May;21(5):507-14. PMID: 22392882.
No drug comparison of interest

Belhadj M, Dahaoui A, Jamoussi H, et al. Exploring insulin analogue safety and effectiveness in a Maghrebian cohort with type 2 diabetes: Results from the A1chieve study. Diabetes Research and Clinical Practice. 2013;101(SUPPL.1):S4-S14.
Does not meet study design criteria

Bell K, Hardy E, De Bruin T, et al. The effect of dapagliflozin on hedis performance measures of hba1c in patients with type 2 diabetes mellitus. Value in Health. 2012;15(4):A171-A2.
Meeting abstract

Bellary S. For type 2 diabetes poorly controlled by metformin monotherapy, the addition of any non-insulin antidiabetic drug reduces HbA1c to a similar extent, but with differing effects on weight and hypoglycaemic risk. Evidence-Based Medicine. 2011;16(2):39-40.
No original data

Bellows B, McAdam-Marx C, Unni S, et al. 12-month A1c and weight outcomes by drug

class in treatment naive patients with type 2 diabetes. Journal of Managed Care Pharmacy. 2012;18(2):157.
Meeting abstract

Bellows BK, Ye X, Unni S, et al. Impact of anti-diabetic drug selection on weight change and hba1c outcomes in treatment naive patients with type 2 diabetes. Diabetes. 2012;61((Bellows B.K.; Ye X.; Unni S.; Mukherjee J.; Iloeje U.H.; McAdam-Marx C.) Salt Lake City, United States):A236-A7.
Meeting abstract

Bensimon L, Yin H, Suissa S, et al. The use of metformin in patients with prostate cancer and the risk of death. Cancer Epidemiol Biomarkers Prev. 2014 Oct;23(10):2111-8. PMID: 25017246.
No drug comparison of interest

Berard E, Bongard V, Arveiler D, et al. 14-year risk of all-cause mortality according to hypoglycemic drug exposure in a general population. European Heart Journal. 2011;32((Berard E.; Bongard V.; Ruidavets J.B.) University Hospital of Toulouse, Department of Epidemiology, Inserm UMR1027, Toulouse, France):973-4.
Meeting abstract

Berberoglu Z, Yazici AC, Bayraktar N, et al. Rosiglitazone decreases fasting plasma peptide YY3-36 in type 2 diabetic women: a possible role in weight gain? Acta Diabetol. 2012 Dec;49 Suppl 1:S115-22. PMID: 22101910.
No drug comparison of interest

Berberoglu Z, Yazici AC, Demirag NG. Effects of rosiglitazone on bone mineral density and remodelling parameters in Postmenopausal diabetic women: a 2-year follow-up study. Clin Endocrinol (Oxf). 2010 Sep;73(3):305-12. PMID: 20148906.
No drug comparison of interest; Placebo-controlled trial

Bergenstal R, Wysham C, Yan P, et al. Duration-2: Exenatide once weekly demonstrated significant glycaemic control and weight reduction compared to sitagliptin or pioglitazone after 26 weeks of treatment. Diabetic Medicine. 2010;27(2):5.
Meeting abstract

Bergenstal R, Wysham C, Yan P, et al. DurAtion-2: Exenatide once weekly demonstrated superior glycemic control and weight reduction compared to sitagliptin or pioglitazone after 26 weeks of treatment. Diabetes. 2009;58((Bergenstal R.; Wysham C.; Yan P.; Macconell L.; Malloy J.; Porter L.)):LB2-LB3.
Meeting abstract

Bergenstal RM, Li Y, Porter TK, et al. Exenatide once weekly improved glycaemic control, cardiometabolic risk factors and a composite index of an HbA1c < 7%, without weight gain or hypoglycaemia, over 52 weeks. Diabetes Obes Metab. 2013 Mar;15(3):264-71. PMID: 23078638.
No drug comparison of interest; Does not meet study design criteria

Bergenstal RM, Rosenstock J, Arakaki RF, et al. A randomized, controlled study of once-daily LY2605541, a novel long-acting basal insulin, versus insulin glargine in basal insulin-treated patients with type 2 diabetes. Diabetes Care. 2012 Nov;35(11):2140-7. PMID: 22787177.
No drug comparison of interest

Berria R, Rosenstock J, Silberman C, et al. Weight loss and associated changes in glycaemic control and cardiovascular biomarkers in patients with type 2 diabetes mellitus receiving incretin therapies in a

large cohort database. Diabetologia. 2009;52(S1):S297.
Meeting abstract

Berstein LM, Boyarkina MP, Teslenko SY. Familial diabetes is associated with reduced risk of cancer in diabetic patients: a possible role for metformin. Med Oncol. 2012 Jun;29(2):1308-13. PMID: 21298495.
Does not apply

Berthet S, Olivier P, Montastruc JL, et al. Drug safety of rosiglitazone and pioglitazone in France: a study using the French PharmacoVigilance database. BMC Clin Pharmacol. 2011;11:5. PMID: 21609444.
Background medications; No drug comparison of interest

Bertrand OF, Poirier P, Rodes-Cabau J, et al. Cardiometabolic effects of rosiglitazone in patients with type 2 diabetes and coronary artery bypass grafts: A randomized placebo-controlled clinical trial. Atherosclerosis. 2010 Aug;211(2):565-73. PMID: 20594555.
Background medications

Best JD, Drury PL, Davis TM, et al. Glycemic control over 5 years in 4,900 people with type 2 diabetes: real-world diabetes therapy in a clinical trial cohort. Diabetes Care. 2012 May;35(5):1165-70. PMID: 22432105.
Does not account for confounding; No drug comparison of interest

Best JH, Hoogwerf BJ, Herman WH, et al. Risk of cardiovascular disease events in patients with type 2 diabetes prescribed the glucagon-like peptide 1 (GLP-1) receptor agonist exenatide twice daily or other glucose-lowering therapies: a retrospective analysis of the LifeLink database. Diabetes Care. 2011 Jan;34(1):90-5. PMID: 20929995.
No drug comparison of interest

Best JH, Hoogwerf BJ, Pelletier EM, et al. Risk of cardiovascular events in patients with type 2 diabetes treated with exenatide or other glucose-lowering therapies: A retrospective analysis of the LifeLinkTM database. Diabetologia. 2010;53((Best J.H.; Wenten M.) Medical Research, Amylin Pharmaceuticals, San Diego, United States):S333.
Meeting abstract

Best JH, Little W, Chiquette E, et al. The risk of heart failure among patients receiving exenatide versus other glucose-lowering medications for type 2 diabetes: A matched retrospective cohort analysis of the GE healthcare electronic medical record database. Diabetes. 2011;60((Best J.H.; Little W.; Chiquette E.; Saunders W.B.) San Diego, United States):A311.
Meeting abstract

Best JH, Pelletier E, Hoogwerf BJ, et al. Risk of cardiovascular events in patients with diabetes treated with exenatide or thiazolidinediones: A retrospective analysis of the pharmetrics database. Value in Health. 2010;13(3):A56.
Meeting abstract

Best JH, Rubin RR, Peyrot M, et al. Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment. Diabetes Care. 2011 Feb;34(2):314-9. PMID: 21270189.
No outcome of interest

Best JH, Wintle M, Saunders WB, et al. Glycemic outcomes among patients receiving exenatide bid or liraglutide for type 2 diabetes in clinical practice: A

retrospective analysis of the ge centricity emr data. Value in Health. 2011;14(7):A473.
Meeting abstract

Best JH, Yan P, Malloy J. DURATION 2: Weight-related quality of life, psychological well-being, and satisfaction with exenatide once weekly compared to sitagliptin or piaglitazone after 26 weeks of treatment. Diabetologia. 2009;52(S1):S292-S3.
Meeting abstract

Bethel MA, Green JB, Milton J, et al. Regional, age and sex differences in baseline characteristics of patients enrolled in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Diabetes Obes Metab. 2015 Jan 20PMID: 25600421.
Background medications

Bhushan R, Elkind-Hirsch KE, Bhushan M, et al. Improved glycemic control and reduction of cardiometabolic risk factors in subjects with type 2 diabetes and metabolic syndrome treated with exenatide in a clinical practice setting. Diabetes Technol Ther. 2009 Jun;11(6):353-9. PMID: 19459763.
Background medications; No drug comparison of interest

Bi Y, Yang H, Zhu D, et al. Effects of exenatide, insulin, and pioglitazone on liver fat content and body fat distributions in newly diagnosed subjects with type 2 diabetes. Diabetes. 2014;63((Bi Y.; Yang H.; Zhu D.; Weng J.) Nanjing, China, Guangzhou, China):A459.
Meeting abstract

Bilezikian J, Kravitz B, Lewiecki EM, et al. Effects of rosiglitazone on bone: Assessing qct parameters in a mechanistic study in postmenopausal women with type 2 diabetes mellitus. Journal of Bone and Mineral Research. 2010;25((Bilezikian J.) Columbia University, College of Physicians and Surgeons, United States):S143.
Meeting abstract

Blak BT, Rigney U, Ycas J, et al. Baseline characteristics, weight and glycaemic change among patients in the United Kingdom with type 2 diabetes mellitus (T2DM) prescribed a new antidiabetic treatment class in a real world setting. Value in Health. 2013;16(7):A432.
Meeting abstract

Blickensderfer A, Pencek R, Li Y, et al. Exenatide once weekly: A retrospective analysis of pooled exenatide clinical trial efficacy data stratified by race, age, duration of diabetes, BMI and gender. Diabetologia. 2011;54((Blickensderfer A.; Pencek R.; Li Y.; Brunell S.) Amylin Pharmaceuticals, Inc., San Diego, United States):S315.
Meeting abstract

Blin P, Lassalle R, Dureau C, et al. Insulin glargine and risk of cancer: A cohort study in the french national healthcare insurance database. Pharmacoepidemiology and Drug Safety. 2012;21((Blin P.; Lassalle R.; Dureau C.; Ambrosino B.; Bernard M.-A.; Abouelfath A.; Gin H.; Pariente A.; Droz-Perroteau C.; Moore N.) Univ. Bordeaux, Bordeaux, France):8.
Meeting abstract

Blin P, Lassalle R, Dureau-Pournin C, et al. Insulin glargine and risk of cancer: a cohort study in the French National Healthcare Insurance Database. Diabetologia. 2012 Mar;55(3):644-53. PMID: 22222504.
No drug comparison of interest

Blonde L, Pencek R, MacConell L. Association among weight change, glycemic control, and markers of cardiovascular risk with exenatide once weekly: a pooled analysis of patients with type 2 diabetes.

Cardiovasc Diabetol. 2015 Feb 3;14(1):12. PMID: 25645567.
No drug comparison of interest

Blonde L, Rosenstock J, Sesti G, et al. Liraglutide provides superior glycaemic control vs exenatide when added to metformin and/or sulphonylurea (SU) in type 2 diabetes (T2DM). Journal of Diabetes. 2009;1((Blonde L.) Oschner Diabetes Research Unit, New Orleans, United States):A24.
Meeting abstract

Blonde L, Woo V, Mathieu C, et al. Achievement of diabetes-related treatment goals with canagliflozin (CANA) in patients with type 2 diabetes mellitus (T2DM). Diabetes. 2014;63((Blonde L.; Woo V.; Mathieu C.; Yee J.; Vijapurkar U.; Meininger G.) New Orleans, LA, Winnipeg, MB, Canada, Leuven, Belgium, Raritan, NJ):A284.
Meeting abstract

Bloomgarden ZT. Type 2 diabetes: Uses of thiazolidinediones and insulin. Diabetes Care. 2011;34(2):e11-e6.
No original data

Bloomgren G, Dore D, Patterson R, et al. Incidence of acute pancreatitis in exenatide initiators compared to other antidiabetic drug initiators: A retrospective, cohort study. Diabetes. 2009;58((Bloomgren G.; Dore D.; Patterson R.; Noel R.; Braun D.; Seeger J.)).
Meeting abstract

Bo S, Ciccone G, Rosato R, et al. Cancer mortality reduction and metformin: a retrospective cohort study in type 2 diabetic patients. Diabetes Obes Metab. 2012 Jan;14(1):23-9. PMID: 21812892.
No drug comparison of interest; Background medications

Boardman MK, Hanefeld M, Kumar A, et al. DURATION-4: Improvements in glucose control and cardiovascular risk factors in patients with type 2 diabetes treated with exenatide once weekly, metformin, pioglitazone, or sitagliptin. Diabetologia. 2011;54((Boardman M.K.; Northrup J.; Chan M.) Eli Lilly and Company, Indianapolis, United States):S314.
Meeting abstract

Bode B, DeFronzo R, Bergenstal R, et al. Effect of liraglutide 3.0/1.8 mg on body weight and cardiometabolic risk factors in overweight/obese adults with type 2 diabetes: SCALE diabetes randomised, double-blind, 56-week trial. Diabetologia. 2014;57(1):S83.
Meeting abstract

Bode B, Stenlof K, Harris S, et al. Long-term efficacy and safety of canagliflozin (CANA) in older patients with type 2 diabetes mellitus (T2DM) over 104 weeks. Diabetes. 2014;63((Bode B.; Stenlof K.; Harris S.; Sullivan D.; Fung A.; Usiskin K.) Atlanta, GA, Gothenburg, Sweden, London, ON, Canada, Raritan, NJ):A71.
Meeting abstract

Bode B, Stenlof K, Harris S, et al. Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes. Diabetes Obes Metab. 2015 Mar;17(3):294-303. PMID: 25495720.
Placebo-controlled trial; No drug comparison of interest

Bode B, Stenlof K, Sullivan D, et al. Efficacy and safety of canagliflozin (CANA), a sodium glucose cotransporter 2 inhibitor (SGLT2), in older subjects with type 2 diabetes mellitus. Diabetologia. 2012;55((Bode B.) Atlanta Diabetes Associates, Atlanta, United States):S315.

Meeting abstract

Bode B, Stenlof K, Sullivan D, et al. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hosp Pract (1995). 2013;41(2):72-84.
Background medications; No drug comparison of interest

Bode BW, Brett J, Falahati A, et al. Comparison of the efficacy and tolerability profile of liraglutide, a once-daily human GLP-1 analog, in patients with type 2 diabetes >/=65 and <65 years of age: a pooled analysis from phase III studies. Am J Geriatr Pharmacother. 2011 Dec;9(6):423-33. PMID: 22055210.
No drug comparison of interest; Background medications

Bode BW, Testa MA, Magwire M, et al. Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. Diabetes Obes Metab. 2010 Jul;12(7):604-12. PMID: 20590735.
No outcome of interest

Bodmer M, Meier C, Krahenbuhl S, et al. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care. 2010 Jun;33(6):1304-8. PMID: 20299480.
No drug comparison of interest

Bolinder J, Ljunggren O, Johansson L, et al. Dapagliflozin produces long-term reductions in body weight, waist circumference and total fat mass in patients with type 2 diabetes inadequately controlled on metformin. Diabetologia. 2012;55((Bolinder J.) Karolinska Institute, Stockholm, Sweden):S308.

Meeting abstract

Bolliger D, Seeberger MD, Lurati Buse G, et al. The influence of pre-admission hypoglycaemic therapy on cardiac morbidity and mortality in type 2 diabetic patients undergoing major non-cardiac surgery: A prospective observational study. Anaesthesia. 2012;67(2):149-57.
Background medications; No drug comparison of interest

Bonds DE, Miller ME, Dudl J, et al. Severe hypoglycemia symptoms, antecedent behaviors, immediate consequences and association with glycemia medication usage: Secondary analysis of the ACCORD clinical trial data. BMC Endocrine Disorders. 2012;12((Bonds D.E., bondsde@nhlbi.nih.gov) National Heart Lung and Blood Institute, National Institute of Health, Bethesda, MD, United States).
No drug comparison of interest

Bonora E, Minervini G, Cook W, et al. Saxagliptin reduces A1C and is well tolerated in patients with type 2 diabetes and high framingham cardiovascular risk or albuminuria. Endocrine Practice. 2014;20(1):34A-5A.
Meeting abstract

Bosco JL, Antonsen S, Sorensen HT, et al. Metformin and incident breast cancer among diabetic women: a population-based case-control study in Denmark. Cancer Epidemiol Biomarkers Prev. 2011 Jan;20(1):101-11. PMID: 21119073.
No drug comparison of interest

Bosi E, Ellis G, Moneuse P, et al. Addition of alogliptin vs uptitration of pioglitazone dose in type 2 diabetes mellitus patients on metformin plus pioglitazone therapy. Diabetologia. 2010;53((Bosi E.) Istituto

Scientifico San Raffaele, Milano, Italy):S328-S9.
Meeting abstract

Boule NG, Kenny GP, Larose J, et al. Does metformin modify the effect on glycaemic control of aerobic exercise, resistance exercise or both? Diabetologia. 2013 Nov;56(11):2378-82. PMID: 23975325.
Does not apply; No drug comparison of interest

Bouzamondo H, Karyekar C, Berglind N, et al. Saxagliptin (SAXA) vs Glipizide (GLIP) as add-on therapy to metformin (MET) for type 2 diabetes (T2D): Assessment of HbA1c, hypoglycemia, and weight gain. Diabetes. 2011;60((Bouzamondo H.; Karyekar C.; Berglind N.; Allen E.) Princeton, United States):A305.
Meeting abstract

Bowker S, Yasui Y, Veugelers P, et al. Effect of glitazones on cancer mortality in type 2 diabetes. Canadian Journal of Diabetes. 2009;33(3):264.
Meeting abstract

Bowker SL, Yasui Y, Veugelers P, et al. Glucose-lowering agents and cancer mortality rates in type 2 diabetes: assessing effects of time-varying exposure. Diabetologia. 2010 Aug;53(8):1631-7. PMID: 20407744.
Background medications; No drug comparison of interest

Boyko EJ, Wheeler S, Moore K, et al. Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea, or rosiglitazone monotherapy. Diabetes. 2013;62((Boyko E.J.; Wheeler S.; Moore K.; Forsberg C.W.; Riley K.; Floyd J.S.; Smith N.L.) Seattle, United States):A405.
Meeting abstract

Boyle J, Fisher M. The addition of insulin to metformin and sulphonylureas: Results of the 4-T study. Practical Diabetes International. 2010;27(1):5-6.
No original data

Brady EM, Davies MJ, Gray LJ, et al. A randomized controlled trial comparing the GLP-1 receptor agonist liraglutide to a sulphonylurea as add on to metformin in patients with established type 2 diabetes during Ramadan: the Treat 4 Ramadan Trial. Diabetes Obes Metab. 2014 Jun;16(6):527-36. PMID: 24373063.
Background medications; No drug comparison of interest

Brady EM, Davies MJ, Gray LJ, et al. Treat 4 Ramadan trial: A randomised control trial comparing liraglutide vs a sulphonylurea as add-on to metformin in patients with established type 2 diabetes. Diabetologia. 2013;56((Brady E.M.) Leicester Diabetes Centre, University of Leicester, Leicester, United Kingdom):S371.
Meeting abstract

Brake JA, Hopkins M, Greenwood A, et al. First three months data from an observational study in people with diabetes commenced on exenatide within a large diabetes centre in both insulin treated and insulin naive patients. Diabetic Medicine. 2009;26((Brake J.A.; Hopkins M.; Greenwood A.; Spelman S.; Brame C.) Diabetes Centre, Royal Liverpool and Broadgreen University Hospital Trust, Liverpool, United Kingdom):142.
Meeting abstract

Bravis V, Hui E, Gohel B, et al. Impact of the READ (Ramadan focused Education and Awareness in Diabetes) programme on HbA1c, weight and hypoglycaemia. Diabetologia. 2009;52(S1):S388-S9.
Meeting abstract

Bray GA, Smith SR, Banerji M, et al. Effect of pioglitazone on body fat and bone mineral content in the act now trial. Diabetes. 2012;61((Bray G.A.; Smith S.R.; Banerji M.; Tripathy D.; Buchanan T.; Kitabchi A.E.; Henry R.; Stentz F.B.; Musi N.; Schwenke D.C.; Reaven P.; Defronzo R.A.) Baton Rouge, United States):A236.
Meeting abstract

Breunig IM, Shaya FT, McPherson ML, et al. Development of heart failure in medicaid patients with type 2 diabetes treated with pioglitazone, rosiglitazone, or metformin. J Manag Care Pharm. 2014 Sep;20(9):895-903. PMID: 25166288.
Background medications

Brixner D, McAdam-Marx C, Ye X, et al. 18 Month A1C and weight outcomes of exenatide therapy in patients with type-2 diabetes in a real-world study. Value in Health. 2009;12(3):A97.
Meeting abstract

Brodovicz KG, Kou TD, Alexander CM, et al. Recent trends in the characteristics of patients prescribed sitagliptin and other oral antihyperglycaemic agents in a large U.S. claims database. Int J Clin Pract. 2013 May;67(5):449-54. PMID: 23574104.
Does not apply

Bron M, Chen K, Cheng D, et al. Comparison of clinical and economic outcomes associated with dpp4 inhibitors (DPP4I) versus sulfonylurea (SU) in combination with metformin (MET) or pioglitazone (PIO) for the treatment of type 2 diabetes mellitus (T2DM). Value in Health. 2012;15(7):A661-A2.
Meeting abstract

Bron M, Marynchenko M, Yang H, et al. Hypoglycaemia in adult vs. elderly type 2 diabetes mellitus patients: Risks, costs, and impact on treatment persistence in a U.S. population. Diabetologia. 2011;54((Bron M.; Yang Y.) Global Health Economics and Outcomes Research, Takeda Pharmaceuticals International, Inc., Deerfield, United States):S266.
Meeting abstract

Bron M, Marynchenko M, Yang H, et al. Hypoglycemia in adult vs elderly type 2 diabetes mellitus patients: Risks, costs, and impact on treatment persistence. Diabetes. 2011;60((Bron M.; Marynchenko M.; Yang H.; Yang Y.; Wu E.; Peng A.) Deerfield, United States):A323.
Meeting abstract

Bron M, Marynchenko M, Yang H, et al. Hypoglycemia, treatment discontinuation, and costs in patients with type 2 diabetes mellitus on oral antidiabetic drugs. Postgrad Med. 2012 Jan;124(1):124-32. PMID: 22314122.
Background medications

Brouwer ES, West SL, Kluckman M, et al. Initial and subsequent therapy for newly diagnosed type 2 diabetes patients treated in primary care using data from a vendor-based electronic health record. Pharmacoepidemiol Drug Saf. 2012 Sep;21(9):920-8. PMID: 22250059.
No outcome of interest

Brown B, Sharp P. Predictive factors in glycaemic response to exenitide and sitagliptin treatment. Diabetic Medicine. 2009;26((Brown B.; Sharp P.) Department of Diabetes, Southampton General Hospital, Southampton, United Kingdom):139.
Meeting abstract

Bruderer SG, Bodmer M, Jick SS, et al. Incidence of and risk factors for severe hypoglycaemia in treated type 2 diabetes

mellitus patients in the UK - a nested case-control analysis. Diabetes Obes Metab. 2014 Feb 25PMID: 24612200.
No drug comparison of interest; Does not meet study design criteria

Bruderer SG, Jick SS, Bader G, et al. Incidence of and risk factors for severe hypoglycemia in treated type 2 diabetes mellitus patients in the United Kingdom. International Journal of Clinical Pharmacy. 2013;35(6):1333-4.
Meeting abstract

Bruhn C. Treatment of type 2 diabetes: Exenatide for once weekly application. Deutsche Apotheker Zeitung. 2011;151(26):39-40.
No original data

Brunell SC, Pencek R, Li Y, et al. Exenatide once weekly was associated with improved glycemic control regardless of baseline body weight. Diabetes. 2012;61((Brunell S.C.; Pencek R.; Li Y.; Hoogwerf B.J.) San Diego, United States):A297.
Meeting abstract

Bryzinski B, Allen E, Cook W, et al. Saxagliptin efficacy and safety in patients with type 2 diabetes receiving concomitant statin therapy. J Diabetes Complications. 2014 Nov-Dec;28(6):887-93. PMID: 25168266.
Placebo-controlled trial

Bunck MC, Cornér A, Eliasson B, et al. Effects of exenatide on measures of ?-cell function after 3 years in metformin-treated patients with type 2 diabetes. Diabetes care; 2011. p. 2041-7.
Received more than the FDA-approved dose of exenatide

Bunck MC, Corner A, Eliasson B, et al. Effects of exenatide on measures of beta-cell function after 3 years in metformin-treated patients with type 2 diabetes. Diabetes Care. 2011 Sep;34(9):2041-7. PMID: 21868779.
Received more than the FDA-approved dose of exenatide

Bunck MC, Corner A, Eliasson B, et al. Extended, 3-year, exenatide therapy shows sustainable effects on beta cell disposition index in metformin treated patients with type 2 diabetes. Diabetologia. 2010;53((Bunck M.C.; Heine R.J.; Diamant M.) Department of Endocrinology/Diabetes Center, VU university medical center, Amsterdam, Netherlands):S338.
Meeting abstract

Bunck MC, Diamant M, Corner A, et al. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes Care. 2009 2009 May;32(5):762-8.
Received more than the FDA-approved dose of exenatide

Bunck MC, Corner A, Eliasson B, et al. One year exenatide therapy, compared with insulin glargine, reduces postprandial oxidative stress in metformin-treated patients with type 2 diabetes. Diabetes. 2009;58((Bunck M.C.; Corner A.; Eliasson B.; Wu Y.; Shaginian R.M.; Yan P.; Heine R.J.; Smith U.; Yki-Jarvinen H.; Taskinen M.-R.; Diamant M.)).
Meeting abstract

Bunck MC, Diamant M, Eliasson B, et al. Beneficial changes on body composition and circulating adiponectin and hsCRP Levels following one year of exenatide therapy, compared with insulin glargine, in metformin-treated patients with type 2 diabetes. Diabetes. 2009;58((Bunck M.C.; Diamant M.; Eliasson B.; Corner A.; Wu Y.;

Shaginian R.M.; Yan P.; Taskinen M.-R.; Heine R.J.; Yki-Jarvinen H.; Smith U.)).
Meeting abstract

Burant C, Fleck P, Wilson C, et al. Effect of alogliptin combined with pioglitazone on beta cell function and insulin resistance in metformin-treated patients with type 2 diabetes. Diabetologia. 2009;52(S1):S314-S5.
Meeting abstract

Burant CF, Viswanathan P, Marcinak J, et al. TAK-875 versus placebo or glimepiride in type 2 diabetes mellitus: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2012 Apr 14;379(9824):1403-11. PMID: 22374408.
Meeting abstract

Burr N, Talboys R, Savva S, et al. Type 2 diabetes as a positive risk factor in the aetiology of cholangiocarcinoma: A case-control study in two UK centres. Gut. 2012;61((Burr N.; Rushbrook S.; Phillips M.; Hart A.) Department of Gastroenterology, Norfolk and Norwich University Hospital, Norwich, United Kingdom):A220-A1.
Meeting abstract

Buse J, Sesti G, Schmidt WE, et al. Glycaemic control improves in type 2 diabetes patients when switching from twice-daily exenatide to once-daily liraglutide. Canadian Journal of Diabetes. 2009;33(3):290.
Meeting abstract

Buse JB, Garber A, Rosenstock J, et al. Liraglutide treatment is associated with a low frequency and magnitude of antibody formation with no apparent impact on glycemic response or increased frequency of adverse events: results from the Liraglutide Effect and Action in Diabetes (LEAD) trials. J Clin Endocrinol Metab. 2011 Jun;96(6):1695-702. PMID: 21450987.
Does not apply; Background medications

Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013 Jan 12;381(9861):117-24. PMID: 23141817.
Background medications

Buse JB, Nauck MA, Forst T, et al. Efficacy and safety of exenatide once weekly versus liraglutide in subjects with type 2 diabetes (DURATION-6): A randomised, open-label study. Diabetologia. 2011;54((Buse J.B.) Endocrinology, University of North Carolina, School of Medicine, Chapel Hill, United States):S38.
Meeting abstract

Buse JB, Peters A, Russell-Jones D, et al. Is insulin the most effective injectable antihyperglycaemic therapy? Diabetes Obes Metab. 2015 Feb;17(2):145-51. PMID: 25323312.
No drug comparison of interest

Buse JB, Wolffenbuttel BHR, Herman WH, et al. The DURAbility of basal versus lispro mix 75/25 insulin efficacy (DURABLE) trial: Comparing the durability of lispro mix 75/25 and glargine. Diabetes Care. 2011;34(2):249-55.
No drug comparison of interest; Background medications

Buysschaert M, Claessens A, Damoiseaux P, et al. Short and medium term effects of exenatide treatment in a cohort of type 2 diabetic patients: Results of a multicentric study within the diabetologists network of UCL. Louvain Medical. 2010;129(2):49-53.
No drug comparison of interest; Does not meet study design criteria

Cai B, Katz L, Alexander CM, et al. Characteristics of patients prescribed sitagliptin and other oral antihyperglycaemic agents in a large US claims database. Int J Clin Pract. 2010 Nov;64(12):1601-8. PMID: 20946268.
No drug comparison of interest

Calvo Romero JM, Ramiro Lozano JM. Vitamin B(12) in type 2 diabetic patients treated with metformin. Endocrinol Nutr. 2012 Oct;59(8):487-90. PMID: 22981397.
Does not meet study design criteria

Camisasca R, Bron M, Fleck P, et al. Alogliptin superior to glipizide in composites of a1c reduction, no hypoglycemia, and no weight gain in patients with T2DM. Diabetes. 2014;63((Camisasca R.; Bron M.; Fleck P.; Wilson C.; Del Prato S.) London, United Kingdom, Deerfield, IL, Pisa, Italy):A269.
Meeting abstract

Campia U, Barac A, Matuskey LA, et al. Oral hypoglycemic treatment may lower vascular endothelin-1 activity in type 2 diabetic patients: A pilot study. Arteriosclerosis, Thrombosis, and Vascular Biology. 2010;30(11):e260.
Meeting abstract

Carney GA, Bassett K, Wright JM, et al. Is thiazolidinediones use a factor in delaying the need for insulin therapy in type 2 patients with diabetes? A population-based cohort study. BMJ Open. 2012;2(6)PMID: 23148347.
No outcome of interest

Cefalu WT, Gause-Nilsson IA, De Bruin TW, et al. Long-term efficacy and safety of dapagliflozin in patients with type 2 diabetes, cardiovascular disease, and hypertension. Diabetes. 2014;63((Cefalu W.T.; Gause-Nilsson I.A.; De Bruin T.W.; Sugg J.E.; Parikh S.J.; Johnsson E.) Baton Rouge, LA, Molndal, Sweden, Wilmington, DE):A286.
Meeting abstract

Cefalu WT, Leiter LA, Debruin TW, et al. Dapagliflozin treatment for type 2 diabetes mellitus patients with comorbid cardiovascular disease and hypertension. Diabetes. 2012;61((Cefalu W.T.; Leiter L.A.; Debruin T.W.; Gausenilsson I.; Sugg J.; Parikh S.J.) Baton Rouge, United States):A271.
Meeting abstract

Cerdas S, Leiter LA, Blonde L, et al. Glycaemic efficacy of canagliflozin by baseline HbA1c and known duration of type 2 diabetes mellitus. Diabetologia. 2014;57(1):S344.
Meeting abstract

Chaiteerakij R, Baichoo E, Roberts LR. Metformin use improves survival of cholangiocarcinoma (CC) patients with type II diabetes (DM). Hepatology. 2013;58(4):331A-2A.
Meeting abstract

Chakraborty A, Chowdhury S, Bhattacharyya M. Effect of metformin on oxidative stress, nitrosative stress and inflammatory biomarkers in type 2 diabetes patients. Diabetes Res Clin Pract. 2011 Jul;93(1):56-62. PMID: 21146883.
Placebo-controlled trial

Chakreeyarat S, Saetung S, Chailurkit LO, et al. Elevated vitamin D status in postmenopausal women on thiazolidinediones for type 2 diabetes. Endocrine. 2011 Jun;39(3):278-82. PMID: 21069575.
No drug comparison of interest

Chang CH, Chang YC, Lin JW, et al. Comparative effectiveness of several second-line dual oral antidiabetic combinations in reducing cardiovascular events in type 2 diabetes-a nationwide study. Diabetes. 2014;63((Chang C.-H.; Chang Y.-C.; Lin J.-W.; Chen S.-T.; Lai M.; Chuang L.-M.) Taipei, Taiwan):A611.
Meeting abstract

Chang CH, Lin JW, Wu LC, et al. Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. Hepatology. 2012 May;55(5):1462-72. PMID: 22135104.
No drug comparison of interest; Background medications

Chang CH, Lin JW, Wu LC, et al. Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. J Clin Endocrinol Metab. 2012 Jul;97(7):E1170-5. PMID: 22563104
No drug comparison of interest

Chao TF, Leu HB, Huang CC, et al. Thiazolidinediones can prevent new onset atrial fibrillation in patients with non-insulin dependent diabetes. Int J Cardiol. 2012 Apr 19;156(2):199-202. PMID: 21930315.
No drug comparison of interest; Not outcome of interest

Chaudhuri A, Rosenstock J, DiGenio A, et al. Comparing the effects of insulin glargine and thiazolidinediones on plasma lipids in type 2 diabetes: a patient-level pooled analysis. Diabetes Metab Res Rev. 2012 Mar;28(3):258-67. PMID: 22081557.
Background medications; No drug comparison of interest

Chavez AO, Guardado-Mendoza R, Cortez L, et al. Differential effect of pioglitazone, exenatide and combination of pioglitazone and exenatide on adipocyte insulin resistance in type 2 diabetes. Diabetes. 2011;60((Chavez A.O.; Guardado-Mendoza R.; Cortez L.; King J.; Kincade J.; Defronzo R.; Tripathy D.) San Antonio, United States):A678.
Meeting abstract

Chavez AO, Guardado-Mendoza R, King JW, et al. Differential effect of pioglitazone, exenatide and combination of pioglitazone and exenatide on adipocyte insulin resistance in type 2 diabetes. Diabetologia. 2011;54((Chavez A.O.; Guardado-Mendoza R.; King J.W.; Kincade J.; Folli F.; DeFronzo R.A.; Tripathy D.) Diabetes Medicine, University of Texas Health Science Center, San Antonio, United States):S213.
Meeting abstract

Chen DY, Wang SH, Mao CT, et al. Sitagliptin and cardiovascular outcomes in diabetic patients with chronic kidney disease and acute myocardial infarction: A nationwide cohort study. Int J Cardiol. 2014 Dec 3;181C:200-6. PMID: 25528312.
Does not account for confounding; No drug comparison of interest

Chen R, Xu Z, Duan Y, et al. Reaching HbA1c goals with saxagliptin in combination with metformin or sulfonylurea. Diabetologia. 2009;52(S1):S296.
Meeting abstract

Chen SW, Tsan YT, Chen JD, et al. Use of thiazolidinediones and the risk of colorectal cancer in patients with diabetes: a nationwide, population-based, case-control study. Diabetes Care. 2013 Feb;36(2):369-75. PMID: 23043163.
No drug comparison of interest

Chen TM, Lin CC. Metformin associated with lower mortality in diabetic patients

with early stage hepatocellular carcinoma after radiofrequency ablation. Hepatology International. 2012;6(1):222.
Meeting abstract

Chen Y, Ning G, Wang C, et al. Efficacy and safety of linagliptin monotherapy in Asian patients with inadequately controlled type 2 diabetes mellitus: A 24-Week, randomized, phase III clinical trial. Diabetes. 2013;62((Chen Y.; Ning G.; Wang C.; Gong Y.; Woerle H.; Wang W.) Shanghai, China, Hefei, China, Ingelheim, Germany):A302.
Meeting abstract

Cheng YY, Leu HB, Chen TJ, et al. Metformin-inclusive therapy reduces the risk of stroke in patients with diabetes: a 4-year follow-up study. J Stroke Cerebrovasc Dis. 2014 Feb;23(2):e99-105. PMID: 24119365.
Background medications

Cherney D, Von Eynatten M, Lund SS, et al. Sodium glucose cotransporter 2 inhibition with empagliflozin reduces microalbuminuria in patients with type 2 diabetes. Diabetologia. 2014;57(1):S333.
Meeting abstract

Chiang HH, Tseng FY, Wang CY, et al. All-cause mortality in patients with type 2 diabetes in association with achieved hemoglobin A1c, systolic blood pressure, and low-density lipoprotein cholesterol levels. PLoS ONE. 2014;9(10).
Background medications

Chiefari E, Capula C, Vero A, et al. Add-On Treatment with Liraglutide Improves Glycemic Control in Patients with Type 2 Diabetes on Metformin Therapy. Diabetes Technol Ther. 2015 Jul;17(7):468-74. PMID: 25844858.
Does not account for confounding

Chien CY, Fang FM, Huang CC. Improved survival among advanced oral cancer patients taking metformin for diabetes mellitus control. Oral Oncology. 2011;47((Chien C.-Y.) Department of Otolaryngology, Chang Gung Memorial Hospital, Kaohsiung Medical Center, Taiwan):S75-S6.
Meeting abstract

Chilton R, Tikkanen I, Crowe S, et al. Empagliflozin reduces systolic blood pressure in dipper and non-dipper patients with type 2 iabetes and hypertension. Circulation. 2014;130((Chilton R.) Univeristy of Texas, Health Science Cntr, San Antonio, United States).
Meeting abstract

Chilton RJ, MacConell LA, Han JC, et al. Characterization of heart rate increases with glucagon-like peptide-1 agonist therapy. Circulation. 2013;128(22).
Meeting abstract

Chiquette E, Toth PP, Ramirez G, et al. Treatment with exenatide once weekly or twice daily for 30 weeks is associated with changes in several cardiovascular risk markers. Vasc Health Risk Manag. 2012;8:621-9. PMID: 23166441.
No drug comparison of interest

Chirila C, Ziemiecki R, Davenport E, et al. Health-related quality of life analysis for patients with type 2 diabetes mellitus treated with empagliflozin. Value in Health. 2014;17(3):A257-A8.
Meeting abstract

Cho SJ, Kim YI, Kim SY, et al. Long-term metformin use reduces gastric cancer risk in type 2 diabetics without insulin treatment: A nationwide cohort study. Cancer Research. 2014;74(19).

No drug comparison of interest

Chou HC, Chen WW, Hsiao FY. Acute pancreatitis in patients with type 2 diabetes mellitus treated with dipeptidyl peptidase-4 inhibitors: a population-based nested case-control study. Drug Saf. 2014 Jul;37(7):521-8. PMID: 24859164.
No drug comparison of interest; Background medications

Choy-Shan A, Zinn A, Shah B, et al. Effect of rosiglitazone on survival in patients with diabetes mellitus treated for coronary artery disease. Coron Artery Dis. 2012 Aug;23(5):354-8. PMID: 22750913.
No drug comparison of interest

Chraibi A, Ajdi F, Belkhadir J, et al. Safety and effectiveness of insulin analogues in Moroccan patients with type 2 diabetes: A sub-analysis of the A1chieve study. Diabetes Research and Clinical Practice. 2013;101(SUPPL.1):S27-S36.
No drug comparison of interest

Clemens KK, McArthur E, Fleet JL, et al. The risk of pancreatitis with sitagliptin therapy in older adults: a population-based cohort study. CMAJ Open. 2015 Apr-Jun;3(2):E172-81. PMID: 26389095.
Background medications

Colette C, Boegner C, Michel F, et al. Comparative effects of glimepiride and rosiglitazone on glycemic disorders and oxidative stress in type 2 diabetes. Journal of Diabetes. 2009;1((Colette C.; Monnier L.) University Institute of Clinical Research, Montpellier, France):A61.
Meeting abstract

Colhoun HM, Livingstone SJ, Looker HC, et al. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012 Nov;55(11):2929-37. PMID: 22945303.
Background medications

Cook W, Bryzinski B, Slater J, et al. Efficacy and safety of saxagliptin (SAXA) in patients with type 2 diabetes and a history of cardiovascular disease. Diabetologia. 2012;55((Cook W.) Medical Affairs, AstraZeneca, Wilmington, United States):S346.
Meeting abstract

Cook W, Bryzinski B, Slater J, et al. Saxagliptin efficacy and safety in patients with type 2 diabetes mellitus and cardiovascular disease history or cardiovascular risk factors: results of a pooled analysis of phase 3 clinical trials. Postgrad Med. 2013 May;125(3):145-54. PMID: 23748515.
Handsearch

Cooper M, Von Eynatten M, Emser A, et al. Efficacy and safety of linagliptin in patients with type 2 diabetes with or without renal impairment: Results from a global phase 3 program. Diabetes. 2011;60((Cooper M.; Von Eynatten M.; Emser A.; Patel S.; Worle H.J.) Melbourne, Australia):A293.
Meeting abstract

Cotugno M, Nosso G, Saldalamacchia G, et al. Clinical efficacy of bariatric surgery versus liraglutide in patients with type 2 diabetes and severe obesity: a 12-month retrospective evaluation. Acta Diabetol. 2014 Sep 14PMID: 25218924.
Background medications; No drug comparison of interest

Cucinotta D, Caputo S, Mannucci E, et al. Safety and efficacy of insulin aspart and soluble human insulin in Type 2 diabetes mellitus. Minerva Endocrinol. 2012 Dec;37(4):357-66. PMID: 23235191.

No drug comparison of interest

Cuddihy R, Tack CJ, Heise T, et al. Once-daily use of a new generation ultra-long acting basal insulin with a bolus boost in insulin-naive people with type 2 diabetes: Comparison with insulin glargine. Diabetologia. 2010;53((Cuddihy R.) International Diabetes Center, Minneapolis, United States):S389.
Meeting abstract

Cuddihy RM, Russell-Jones D, Hanefeld M, et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes. Diabetes. 2011;60((Cuddihy R.M.; Russell-Jones D.; Hanefeld M.; Kumar A.; Gonzalez J.G.; De Teresa L.; Boardman M.; Chan M.; Wolka A.M.; Porter L.) Minneapolis, United States):A77.
Meeting abstract

Currie CJ, Evans M, Poole CD, et al. Retrospective evaluation of the safety of exogenous insulin in people with type 2 diabetes: Cardiovascular events, stroke, cancers, all-cause mortality and a combined endpoint. Diabetologia. 2011;54((Currie C.J.; Poole C.D.; Morgan C.L.) Department of Public Health, Primary Care Cardiff University, United Kingdom):S311.
Meeting abstract

Currie CJ, Jenkins-Jones S, Mukherjee J, et al. Combination therapy with metformin plus sulfonylureas versus metformin plus DPP-4 inhibitors and risk of all-cause mortality. Diabetologia. 2013;56((Currie C.J.; Morgan C.L.) Department of Primary Care and Public Health, Cardiff University, Cardiff, United Kingdom):S88-S9.
Meeting abstract

Currie CJ, Poole CD, Evans M, et al. Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. J Clin Endocrinol Metab. 2013 Feb;98(2):668-77. PMID: 23372169.
Does not account for confounding

Currie CJ, Poole CD, Jenkins-Jones S, et al. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care. 2012 Feb;35(2):299-304. PMID: 22266734.
Currie CJ. The longest ever randomised controlled trial of insulin glargine: Study design and HbA1c findings. Diabetologia; 2009. p. 2234-5.
Comorbidity

Cusi K, Orsak B, Lomonaco R, et al. Extended treatment with pioglitazone improves liver histology in patients with prediabetes or type 2 diabetes mellitus and NASH. Hepatology. 2013;58(4):248A.
Meeting abstract

D'Alessio D, Haring HU, Charbonnel B, et al. Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. Diabetes Obes Metab. 2015 Feb;17(2):170-8. PMID: 25359159.
No drug comparison of interest; Background medications

Daniele G, Perez-Cadena Z, Chavez-Velasquez A, et al. Low-dose (15 mg/day) pioglitazone treatment improves glycemic and sub-inflammatory state in obese type 2 diabetic subjects in 24 week intervention study. Diabetes. 2012;61((Daniele G.; Perez-Cadena Z.; Chavez-Velasquez A.; Kamath S.; Zuo P.; Chang Z.; Andreozzi F.; Paez A.M.; Fourcaudot M.; Winnier D.; Arya R.; Hansis-Diarte A.; Jenkinson C.; Fanti P.; Gastaldelli A.; Defronzo R.;

Tripathy D.; Folli F.) San Antonio, United States):A274.
Meeting abstract

Danyarova L, Raisova A. Experience of using sitagliptin in Kazakhstan. Diabetes Technology and Therapeutics. 2013;15((Danyarova L.; Raisova A.) Endocrinology, Research Institut of Cardiology and Internal Diseases, Almaty, Kazakhstan):A28-A9.
Meeting abstract

Das P, Das BP, Rauniar GP, et al. Drug utilization pattern and effectiveness analysis in diabetes mellitus at a tertiary care centre in eastern Nepal. Indian J Physiol Pharmacol. 2011 Jul-Sep;55(3):272-80. PMID: 22471235.
Does not apply; No outcome of interest

Davidson JA, Lajara R, Aguilar RB, et al. Efficacy and safety of linagliptin in Hispanic/Latino patients with type 2 diabetes mellitus: a pooled analysis from six randomized placebo-controlled phase 3 trials. BMJ Open Diabetes Res Care. 2014;2(1):e000020. PMID: 25452864.
No drug comparison of interest

Davidson M, McNair D, Mattison D, et al. Clinical and pharmacovigilance approaches for exploring an electronic medical record dataset of Type II diabetics and thiazolidinedione drug safety. European Journal of Epidemiology. 2013;28(1):S133.
Meeting abstract

Davidson MH, Beam CA, Haffner S, et al. Pioglitazone versus glimepiride on coronary artery calcium progression in patients with type 2 diabetes mellitus: a secondary end point of the CHICAGO study. Arterioscler Thromb Vasc Biol. 2010 Sep;30(9):1873-6. PMID: 20576945.
No outcome of interest; No drug comparison of interest

Davies M, Atkin S, Bain SC, et al. Efficacy and safety of liraglutide vs. placebo as add-on to existing diabetes medication in subjects with type 2 diabetes (T2DM) and moderate renal impairment (LIRA-RENAL). Diabetes. 2014;63((Davies M.; Atkin S.; Bain S.C.; Scott D.; Rossing P.; Shamkhalova M.; Bosch-Traberg H.; Syren A.; Umpierrez G.E.) Leicester, United Kingdom, Hull, United King dom, Swansea, United Kingdom, Rosedale, NY, Gentofte, Denmark, Moscow, Russian Federation, Soborg, Denmark, Atlanta, GA):A247-A8.
Meeting abstract

Davies M, Bode BW, Kushner RF, et al. Liraglutide 3.0 mg for weight management in obese/overweight adults with type 2 diabetes: Results from the Scale(trademark) diabetes 56-week randomized, double-blind, placebo-controlled trial. Diabetes. 2014;63((Davies M.; Bode B.W.; Kushner R.F.; Lewin A.J.; Skjoth T.V.; Jensen C.B.; Defronzo R.A.) Leicester, United Kingdom, Atlanta, GA, Chicago, IL, Los Angeles, CA, Bagsvaerd, Denmark, Soborg, Denmark, San Antonio, TX):A26.
Meeting abstract

Davies M, Heller S, Sreenan S, et al. Once-weekly exenatide vs once- or twicedaily insulin detemir: Randomised, openlabel clinical trial of efficacy and safety in patients with Type 2 diabetes inadequately controlled with metformin alone or with sulphonylureas. Diabetic Medicine. 2013;30((Davies M.) CardiovascularSciences, UniversityofLeicester, Leicester, United Kingdom):57-8.
Meeting abstract

Davies M, Nauck M, Bailey T, et al. Better glycaemic control and weight reduction with liraglutide, a once-daily human GLP-1 analogue, compared with sitagliptin, a DPP-4 inhibitor, both in combination with metformin in type 2 diabetes. Diabetic Medicine. 2010;27(2):4-5.
Meeting abstract

Davies M, Nauck M, Bailey T, et al. Liraglutide treatment for 1 year offers more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in type 2 diabetes. Journal of Diabetes. 2011;3((Davies M.) University of Leicester, Leicester, United Kingdom):15.
Meeting abstract

Davies M, Nauck M, Bailey T, et al. The GLP-1 analogue liraglutide provides more effective glycaemic control and weight reduction over one year compared with sitagliptin, a DPP-4 inhibitor, In patients with Type 2 diabetes inadequately controlled with metformin. Diabetic Medicine. 2011;28((Davies M.) Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom):70.
Meeting abstract

Davies M, Pratley R, Montanya E, et al. Liraglutide reduces hba1c to a greater extent than sitagliptin regardless of baseline hba1c. Journal of Diabetes. 2011;3((Davies M.) University of Leicester, Leicester, United Kingdom):185.
Meeting abstract

Davies MJ, Brady EM, Gray LJ, et al. Treat 4 ramadan: A randomised control trial comparing liraglutide vs. A sulphonylurea as add-on to metformin in patients with established type 2 diabetes. Diabetes. 2013;62((Davies M.J.; Brady E.M.; Gray L.J.; Saeed M.; Wasim H.; Khunti K.) Leicester, United Kingdom, Birmingham, United Kingdom):A661.
Meeting abstract

Davies MJ, Pratley RE, Nauck MA, et al. Improved treatment satisfaction in patients with Type 2 diabetes who switched from sitagliptin to liraglutide, both added to metformin. Diabetic Medicine. 2012;29((Davies M.J.) Department of Cardiovascular Sciences, Diabetes Research, University of Leicester, Leicester, United Kingdom):71.
Meeting abstract

de Boer RA, Martens FM, Kuipers I, et al. The effects of the PPAR-gamma agonist pioglitazone on plasma concentrations of circulating vasoactive factors in type II diabetes mellitus. J Hum Hypertens. 2010 Jan;24(1):74-6. PMID: 19847195.
No comparison of interest; Follow-up less than 3 months; Background medications

De Bruin TW, Leiter LA, Cefalu WT, et al. Dapagliflozin in patients with type 2 diabetes and established cardiovascular disease: Hypotension and volume-related safety. Circulation. 2013;128(22).
Meeting abstract

De Fronzo R, Burant CF, Fleck P, et al. Combination alogliptin plus pioglitazone treatment in patients with type 2 diabetes receiving metformin. Canadian Journal of Diabetes. 2009;33(3):257-8.
Meeting abstract

DeFronzo R, Burant C, Fleck P, et al. Effect of alogliptin combined with pioglitazone on glycaemic control in metformin-treated patients with type 2 diabetes. Diabetologia. 2009;52(S1):S295.
Meeting abstract

Defronzo RA, Bode BW, Kushner RF, et al. Effects of liraglutide 3.0 mg cessation on efficacy and safety/ tolerability following a 56-week randomized treatment period in obese/overweight adults with type 2 diabetes (Scale(trademark) diabetes). Diabetes. 2014;63((Defronzo R.A.; Bode B.W.; Kushner R.F.; Lewin A.J.; Skjoth T.V.; Jensen C.B.; Davies M.) San Antonio, TX, Atlanta, GA, Chicago, IL, Los Angeles, CA, Bagsvaerd, Denmark, Soborg, Denmark, Leicester, United Kingdom):A518-A9.
Meeting abstract

Defronzo RA, Burant CF, Fleck P, et al. Effect of alogliptin combined with pioglitazone on glycemic control in metformin-treated patients with type 2 diabetes. Diabetes. 2009;58((Defronzo R.A.; Burant C.F.; Fleck P.; Wilson C.; Mekki Q.; Pratley R.E.)).
Meeting abstract

DeFronzo RA, Fleck PR, Wilson CA, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. Diabetes Care. 2008 Dec;31(12):2315-7. PMID: 18809631.
Placebo-controlled trial

DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care. 2015 Mar;38(3):384-93. PMID: 25583754.
No drug comparison of interest

Defronzo RA, Triplitt C, Qu Y, et al. Effects of exenatide plus rosiglitazone on beta cell function and insulin sensitivity in subjects with type 2 diabetes on metformin. Diabetes. 2009;58((Defronzo R.A.; Triplitt C.; Qu Y.; Lewis M.S.; Gray A.; Maggs D.; Glass L.C.)).
Meeting abstract

Degli Esposti L, Saragoni S, Buda S, et al. Clinical outcomes and health care costs combining metformin with sitagliptin or sulphonylureas or thiazolidinediones in uncontrolled type 2 diabetes patients. Clinicoecon Outcomes Res. 2014;6:463-72. PMID: 25364266.
Background medications

Del Prato S, Barnett AH, Huisman H, et al. Effect of linagliptin monotherapy on glycaemic control and markers of beta-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes Obes Metab. 2011 Mar;13(3):258-67. PMID: 21205122.
No drug comparison of interest; Placebo-controlled trial

Del Prato S, Camisasca R, Wilson C, et al. Durability of the efficacy and safety of alogliptin compared to glipizide over 2 years when used in combination with metformin. Diabetologia. 2013;56((Del Prato S.) UOC Malattie Metaboliche e Diabetologia, Pisa, Italy):S52-S3.
Meeting abstract

Del Prato S, Camisasca R, Wilson C, et al. Durability of the efficacy and safety of alogliptin compared to glipizide when used in combination with metformin: 1 year interim analysis. Diabetes. 2013;62((Del Prato S.; Camisasca R.; Wilson C.; Fleck P.) Pisa, Italy, Deerfield, IL):A274.
Meeting abstract

Del Prato S, Lucchesi D, Pucci L, et al. Effects of pioglitazone on endothelial progenitor cells in type 2 diabetic patients with vascular complications: The splendor study. Diabetes. 2013;62((Del Prato S.;

Lucchesi D.; Pucci L.; Bruno R.; Russo E.; Garofolo M.; Fadini G.; Bornez V.S.; Russo R.; Miccoli R.; Avogaro A.; Ghiadoni L.; Di Pietro C.; Penno G.) Pisa, Italy, Padova, Italy, Rome, Italy):A127.
Meeting abstract

Del Prato S, Nauck M, Rohwedder K, et al. Durability of glycaemic response with dapagliflozin as add-on therapy in type 2 diabetes inadequately controlled with metformin; 4-year data versus glipizide. Diabetologia. 2014;57(1):S345.
Meeting abstract

Del Prato S, Nauck MA, Rohwedder K, et al. Long-term efficacy and safety of add-on dapagliflozin vs add-on glipizide in patients with type 2 diabetes mellitus inadequately controlled with metformin: 2-year results. Diabetologia. 2011;54((Del Prato S.) Endocrinology and Metabolism, University of Pisa, Italy):S348.
Meeting abstract

Del Prato S, Taskinen MR, Owens D, et al. Efficacy and safety of linagliptin in patients with type 2 diabetes and poor glycemic control. Diabetes. 2011;60((Del Prato S.; Taskinen M.-R.; Owens D.; Von Eynatten M.; Emser A.; Patel S.; Woerle H.J.) Pisa, Italy):A293.
Meeting abstract

Delgado E. Outcomes with insulin glargine in patients with type 2 diabetes previously on NPH insulin: Evidence from clinical practice in Spain. International Journal of Clinical Practice. 2012;66(3):281-8.
Background medications; No drug comparison of interest

Derosa G, Putignano P, Bossi AC, et al. Exenatide or glimepiride on insulin resistance in type 2 diabetic patients. Diabetes. 2011;60((Derosa G.; Putignano P.; Bossi A.C.; Bianchi L.; Querci F.; Franzetti I.G.; Guazzini B.; Testori G.; Fogari E.; Maffioli P.) Pavia, Italy):A294.
Meeting abstract

Derosa G, Ragonesi PD, Salvadeo SAT, et al. Effects of exenatide compared to glibenclamide on glycemic control and on insulin resistance in type 2 diabetic patients with metformin therapy. Diabetes. 2009;58((Derosa G.; Ragonesi P.D.; Salvadeo S.A.T.; Ferrari I.; Querci F.; Franzetti I.G.; Gadaleta G.; Ciccarelli L.; Piccinni M.N.; D'Angelo A.; Cicero A.F.G.)).
Meeting abstract

Detournay B, Dejager S, Robert J. Hospitalisation frequency for hypoglycaemia and emergency calls in type 2 diabetes mellitus patients exposed to vildagliptin vs insulin-secretagogues in the French Health Insurance database. Diabetologia. 2014;57(1):S141-S2.
Meeting abstract

Devineni D, Morrow L, Hompesch M, et al. Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. Diabetes Obes Metab. 2012 Jun;14(6):539-45. PMID: 22226086.
No drug comparison of interest

DeVries JH, Meneghini L, Barnett AH, et al. A patient-level analysis of efficacy and hypoglycaemia outcomes across treat-to-target trials with insulin glargine added to oral antidiabetes agents in people with type 2 diabetes. European Endocrinology. 2014;10(1):23-30.
No drug comparison of interest

Dhananjayan R, Srivani Koundinya KS, Malati T, et al. Effect of metformin, glimepiride and gliclazide on intimal medial

thickening of carotid artery in type 2 diabetes mellitus. Biomedicine (India). 2014;34(3):369-73.
Does not report long-term outcomes or adverse events

Dhar K, Chopra VS, Raina RS. Drug prescribing pattern of oral antidiabetic drugs and their comparative efficacy in glycemic control in type-2 diabetes mellitus. International Journal of Pharmaceutical Research. 2013;5(3):33-42.
No outcome of interest

Diamant M, Van Gaal L, Guerci B, et al. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. Lancet Diabetes Endocrinol. 2014 Jun;2(6):464-73. PMID: 24731672.
Background medications; No drug comparison of interest

Diamant M, Van Gaal LF, Stranks SN, et al. Impact of exenatide once weekly and insulin glargine on glucose control and cardiovascular risk f actors in subjects with type 2 diabetes. Diabetologia. 2010;53((Diamant M.) Diabetes Centre, VU University Medical Centre, Amsterdam, Netherlands):S344.
Meeting abstract

Diamant M, VanGaal L, Stranks S, et al. DURATION-3: Changes in cardiovascular risk factors observed in patients with type 2 diabetes after 84-week therapy with exenatide once weekly or insulin glargine. Diabetologia. 2011;54((Diamant M.) Diabetes Center, VU University Medical Center, Amsterdam, Netherlands):S313.
Meeting abstract

Diels J, Angermund R, Schroeder M, et al. The efficacy and effectiveness in HbA1c-lowering is dependent on baseline body mass index (BMI) for sitagliptin but not canagliflozin in the treatment of type 2 diabetes mellitus (T2DM). Value in Health. 2014;17(7):A334.
Meeting abstract

Diop SN, Wade A, Lokrou A, et al. Management of type 2 diabetes in clinical practices in sub-Saharan Africa: Results of the AMAR-AFO study in Senegal and Ivory Cost. Medecine des Maladies Metaboliques. 2013;7(4):363-7.
Does not apply

Distiller LA, Polakow ES, Joffe BI. Type 2 diabetes mellitus and hypothyroidism: the possible influence of metformin therapy. Diabet Med. 2014 Feb;31(2):172-5. PMID: 24151823.
No drug comparison of interest; Does not meet study design criteria

Dittrich S, Bazelier MT, Vestergaard P, et al. Use of biguanides and the risk of colorectal cancer. Pharmacoepidemiology and Drug Safety. 2013;22((Dittrich S.; Stolk L.; Neef K.; De Vries F.) Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht, Netherlands):355-6.
Meeting abstract

Doehner W, Erdmann E, Cairns R, et al. Effects of pioglitazone on body weight in the PROactive study population: The obesity paradox in type 2 DM patents with high risk of cardiovascular events. European Heart Journal. 2009;30((Doehner W.; Anker S.D.) Charite - Campus Virchow-Klinikum, Berlin, Germany):226.
Meeting abstract

Donadon V, Balbi M, Mas MD, et al. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients

with chronic liver disease. Liver Int. 2010 May;30(5):750-8. PMID: 20331505.
Comorbidity

Donadon V, Balbi M, Valent F, et al. Glycated hemoglobin and antidiabetic strategies as risk factors for hepatocellular carcinoma. World J Gastroenterol. 2010 Jun 28;16(24):3025-32. PMID: 20572306.
Does not account for confounding; Background medications

Dore DD, Bloomgren GL, Wenten M, et al. A cohort study of acute pancreatitis in relation to exenatide use. Diabetes Obes Metab. 2011 Jun;13(6):559-66. PMID: 21320263.
No drug comparison of interest; Background medications

Dormuth CR, Carney G, Sutherland J. Delayed progression to insulin in patients with type 2 diabetes mellitus treated with thiazolidinediones: A population-based cohort study. Pharmacoepidemiology and Drug Safety. 2010;19((Dormuth C.R.; Carney G.; Sutherland J.) University of British Columbia, Vancouver, Canada):S191-S2.
Meeting abstract

Dormuth CR, Maclure M, Carney G, et al. Rosiglitazone and myocardial infarction in patients previously prescribed metformin. PLoS One. 2009;4(6):e6080. PMID: 19562036.
Comorbidity; Placebo-controlled trial

Doucet J, Chacra A, Maheux P, et al. Efficacy and safety of saxagliptin in older patients with type 2 diabetes mellitus. Curr Med Res Opin. 2011 Apr;27(4):863-9. PMID: 21323504.
No original data; No drug comparison of interest

Doucet J, Kerlan V, Verges B, et al. LIGHT study: Initiation of long-acting insulin analogues in elderly type 2 diabetic patients. Journal of the American Geriatrics Society. 2010;58((Doucet J.) Rouen University Hospital, Rouen, France):S30-S1.
Meeting abstract

Dover A, Kockum L, Walker J, et al. Efficacy and side effects of liraglutide compared with exenatide therapy. Diabetic Medicine. 2012;29((Dover A.; Kockum L.; Walker J.; Adamson K.) Department of Diabetes, St John's Hospital, Livingston, United Kingdom):69.
Meeting abstract

Drake T, Hire D, Seaquist E. Achieving goal hemoglobin A1C in the standard therapy group of the ACCORD trial. Diabetes. 2013;62((Drake T.; Hire D.; Seaquist E.) Minneapolis, MN, Winston-Salem, NC):A275.
Meeting abstract

Driessen JHM, Van Onzenoort HA, Lalmohamed A, et al. Use of glucagon-like peptide 1 analogues and the risk of fracture in type 2 diabetes patients. Pharmacoepidemiology and Drug Safety. 2013;22((Driessen J.H.M.; Neef K.; De Vries F.) CAPHRI, Maastricht University, Maastricht, Netherlands):513.
Meeting abstract

Dworak M, Gruenberger JB, Bader G, et al. Incidence of cardiovascular events in patients with type 2 diabetes mellitus treated with DPP-4 inhibitors and sulfonylureas in clinical practice in Germany and the UK: A retrospective analysis. Diabetologia. 2012;55((Dworak M.) Novartis Pharma GmbH, Nuernberg, Germany):S323.
Meeting abstract

Echtay A, Tsur A, Hasan MI, et al. Clinical experience with insulin detemir in patients with type 2 diabetes from the near East Countries. Diabetes Therapy. 2013;4(2):399-408.
Background medications

Ekstrom N, Miftaraj M, Svensson AM, et al. Glucose-lowering treatment and clinical results in 163 121 patients with type 2 diabetes: an observational study from the Swedish national diabetes register. Diabetes Obes Metab. 2012 Aug;14(8):717-26. PMID: 22364580.
Does not meet study design criteria

Ekstrom N, Schioler L, Svensson AM, et al. Benefits and risks of glucose-lowering treatments with particular emphasis on metformin: Nationwide epidemiological study. Diabetes. 2012;61((Ekstrom N.; Schioler L.; Svensson A.-M.; Eegolofsson K.; Jonasson J.M.; Zethelius B.; Cederholm J.; Gudbjornsdottir S.; Eliasson B.) Gothenburg, Sweden):A381.
Meeting abstract

Eliasson B, Moller-Goede D, Eeg-Olofsson K, et al. Lowering of postprandial lipids in individuals with type 2 diabetes treated with alogliptin and/or pioglitazone: a randomised double-blind placebo-controlled study. Diabetologia. 2012 Apr;55(4):915-25. PMID: 22237690.
Background medications

Engel S, Arjona Ferreira JC, Guo H, et al. Consistency of HbA1c-lowering effects of sitagliptin vs glipizide in patients with type 2 diabetes and chronic renal insufficiency across a variety of baseline characteristics. Diabetologia. 2012;55((Engel S.; Arjona Ferreira J.C.; Guo H.; Golm G.; Johnson-Levonas A.O.; Kaufman K.; Goldstein B.J.) Merck Sharp and Dohme, Whitehouse Station, United States):S342.
Meeting abstract

Engel SS, Golm GT, Shapiro D, et al. Cardiovascular safety of sitagliptin in patients with type 2 diabetes mellitus: a pooled analysis. Cardiovasc Diabetol. 2013;12:3. PMID: 23286208.
Handsearch

Engel SS, Round E, Golm GT, et al. Safety and tolerability of sitagliptin in type 2 diabetes: pooled analysis of 25 clinical studies. Diabetes Ther. 2013 Jun;4(1):119-45. PMID: 23700194.
No drug comparison of interest

Engel SS, Seck TL, Golm GT, et al. Assessment of AACE/ACE recommendations for initial dual antihyperglycemic therapy using the fixed-dose combination of sitagliptin and metformin versus metformin. Endocr Pract. 2013 Sep-Oct;19(5):751-7. PMID: 23757615.
No original data; No outcome of interest

Engel SS, Teng R, Davies MJ, et al. Influence of baseline glycemic control on sitagliptin-induced weight loss in patients with type 2 diabetes. Diabetes. 2011;60((Engel S.S.; Teng R.; Davies M.J.; Golm G.T.; Katzeff H.; Kaufman K.D.; Goldstein B.J.) Whitehouse Station, United States):A609-A10.
Meeting abstract

Engel SS, Williams-Herman DE, Golm GT, et al. Sitagliptin: review of preclinical and clinical data regarding incidence of pancreatitis. Int J Clin Pract. 2010 Jun;64(7):984-90. PMID: 20412332.
No original data

Engel SS, Xu L, Golm GT, et al. Comparison of treatment with sitagliptin (SITA) or sulfonylurea (SU) in patients with

type 2 diabetes mellitus (T2DM) and mild renal insufficiency. Diabetes. 2013;62((Engel S.S.; Xu L.; Golm G.T.; O'neill E.A.; Kaufman K.D.; Goldstein B.J.) Whitehouse Station, United States):A139.
Meeting abstract

Erdmann E, Song E, Spanheimer R, et al. Observational follow-up of the PROactive study: a 6-year update. Diabetes Obes Metab. 2014 Jan;16(1):63-74. PMID: 23859428.
Background medications

Erdmann E, Song E, Spanheimer R, et al. Pioglitazone and bladder malignancy during observational follow-up of proactive: 6-Year update. Diabetes. 2012;61((Erdmann E.; Song E.; Spanheimer R.; Van A.-R.; De Bruyn T.; Perez A.) Cologne, Germany):A236.
Meeting abstract

Erdmann E, Song E, Spanheimer R, et al. Pioglitazone and macrovascular outcomes during observational follow-up of proactive: 6-year update. Diabetes. 2012;61((Erdmann E.; Song E.; Spanheimer R.; Van A.-R.; De Bruyn T.; Perez A.) Cologne, Germany):A238.
Meeting abstract

Erdmann E, Song E, Spanheimer R, et al. Pioglitazone and macrovascular outcomes during observational followup of PROactive: 6-year update. Diabetologia. 2012;55((Erdmann E.) Medical Clinic III, University Cologne, Germany):S498.
Meeting abstract

Erdmann E, Spanheimer R, Charbonnel B. Pioglitazone and the risk of cardiovascular events in patients with Type 2 diabetes receiving concomitant treatment with nitrates, renin-angiotensin system blockers, or insulin: results from the PROactive study (PROactive 20). J Diabetes. 2010 Sep;2(3):212-20. PMID: 20923486.
Placebo-controlled trial; Background medications

Esbah O, Oksuzoglu B, Eren T, et al. Metformin in diabetic pancreatic cancer patients: Benefit or not-Multicenter experience. Journal of Clinical Oncology. 2013;31(15).
Meeting abstract

Esteghamati A, Afarideh M, Feyzi S, et al. Comparative effects of metformin and pioglitazone on fetuin-A and osteoprotegerin concentrations in patients with newly diagnosed diabetes: A randomized clinical trial. Diabetes Metab Syndr. 2014 Oct 14PMID: 25450818.
No outcome of interest

Esteghamati A, Noshad S, Rabizadeh S, et al. Comparative effects of metformin and pioglitazone on omentin and leptin concentrations in patients with newly diagnosed diabetes: a randomized clinical trial. Regul Pept. 2013 Mar 10;182:1-6. PMID: 23328000.
No outcome of interest

Esteva FJ. Long-term metformin use is associated with decreased risk of breast cancer: Bodmer M, Meier C, Krahenbuhl S, et al (Univ Hosp Basel, Switzerland; et al) Diabetes Care 33:1304-1308, 2010. Breast Diseases. 2011;22(2):133.
No original data; Abstract only

Evans M, McEwan P, O'Shea R, et al. Effectiveness in clinical practice of incretin-based therapies used for the treatment of type 2 diabetes: Results from a national, retrospective, UK case-note survey. Medecine des Maladies Metaboliques. 2014;8(2):177-83.
Non-English language

Faber-Heinemann G. Comparison between clinical efficacy of DPP-4 inhibitors and GLP-1 analogs in type 2 diabetics. Diabetes, Stoffwechsel und Herz. 2012;21(6):357-68.
Does not meet study design criteria

Fadini GP, de Kreutzenberg SV, Mariano V, et al. Optimized glycaemic control achieved with add-on basal insulin therapy improves indexes of endothelial damage and regeneration in type 2 diabetic patients with macroangiopathy: A randomized crossover trial comparing detemir versus glargine. Diabetes, Obesity and Metabolism. 2011;13(8):718-25.
Background medications

Faillie JL, Azoulay L, Patenaude V, et al. Incretin based drugs and risk of acute pancreatitis in patients with type 2 diabetes: Cohort study. BMJ (Online). 2014;348((Faillie J.-L.; Azoulay L.; Patenaude V.; Suissa S., samy.suissa@mcgill.ca) Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC H3T 1E2, Canada).
Other: Class comparison; Does not meet study design criteria

Faillie JL, Babai S, Crepin S, et al. Pancreatitis and use of GLP1 analogs and DPP4 inhibitors: A case/non-case study from the french pharmacovigilance database. Drug Safety. 2013;36(9):916.
Meeting abstract

Fattor B, Cretti A, Cristini M, et al. Treatment with GLP-1 analogue liraglutide is associated with improvement in HbA1c and weight loss in type 2 diabetic patients after early metformin failure. Italian Journal of Medicine. 2014;8((Fattor B.; Cretti A.; Cristini M.; Lintner S.; Monauni T.; Orion G.; Telfser C.; Zardi F.) Servizio di Diabetologia, UO Medicina Interna, Ospedale di Bolzano, Italy):44.
Meeting abstract

Feldman L, Shani M, Efrati S, et al. Association between rosiglitazone use and decline in renal function in patients with type 2 diabetes mellitus. J Nephrol. 2010 May-Jun;23(3):350-6. PMID: 20155725.
No outcome of interest; Background medications

Feng P, Yu DM, Chen LM, et al. Liraglutide reduces the body weight and waist circumference in Chinese overweight and obese type 2 diabetic patients. Acta Pharmacol Sin. 2015 Feb;36(2):200-8. PMID: 25619391.
Single arm; No drug comparison of interest

Ferdinand KC, White WB, Calhoun DA, et al. Effects of the Once-Weekly Glucagon-Like Peptide-1 Receptor Agonist Dulaglutide on Ambulatory Blood Pressure and Heart Rate in Patients With Type 2 Diabetes Mellitus. Hypertension. 2014 Jun 30PMID: 24980665.
Background medications

Ferrannini E, Ramos SJ, Salsali A, et al. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care. 2010 Oct;33(10):2217-24. PMID: 20566676.
Placebo-controlled trial

Ferrannini E, Seman LJ, Seewaldt-Becker E, et al. The potent and highly selective sodium-glucose co-cransporter (SGLT-2) inhibitor BI 10773 is safe and efficacious as monotherapy in patients with type 2 diabetes mellitus. Diabetologia. 2010;53((Ferrannini

E.) Medicine, University of Pisa, Italy):S351.
Meeting abstract

Ferrara A, Lewis JD, Quesenberry CP, Jr., et al. Cohort study of pioglitazone and cancer incidence in patients with diabetes. Diabetes Care. 2011 Apr;34(4):923-9. PMID: 21447664.
No drug comparison of interest

Ferreira JCA, Engel SS, Guo H, et al. Consistency of the A1C-lowering effects of sitagliptin versus glipizide in patients with type 2 diabetes and chronic renal insufficiency across a variety of baseline characteristics. Diabetes. 2012;61((Ferreira J.C.A.; Engel S.S.; Guo H.; Golm G.T.; Johnson-Levonas A.O.; Kaufman K.D.; Goldstein B.J.) Rahway, United States):A281.
Meeting abstract

Ferreira JCA, Engel SS, Guo H, et al. Sitagliptin more effectively achieves a composite endpoint of a1c reduction, no body weight gain, and lack of hypoglycemia in patients with type 2 diabetes and renal insufficiency compared to glipizide. Diabetes. 2012;61((Ferreira J.C.A.; Engel S.S.; Guo H.; Golm G.T.; Sisk C.M.; Kaufman K.D.; Goldstein B.J.) Rahway, United States):A258.
Meeting abstract

Filion KB, Joseph L, Boivin JF, et al. Thiazolidinediones and the risk of incident congestive heart failure among patients with type 2 diabetes mellitus. Pharmacoepidemiol Drug Saf. 2011 Aug;20(8):785-96. PMID: 21671441.
Does not account for confounding

Fiorentino TV, Daniele G, Tripathy D, et al. Low dose pioglitazone-induced reduction in skeletal muscle TACE activity and TNFalpha is associated with an improvement of glycaemic control in type 2 diabetic patients. Diabetologia. 2013;56((Fiorentino T.V.; Daniele G.; Tripathy D.; Perez-Cadena Z.; Chavez-Velasquez A.; Kamath S.; DeFronzo R.A.; Folli F.) Medicine, University of Texas Health Science Center at San Antonio, United States):S249.
Meeting abstract

Fioretto P, De Bruin TW, Johnsson E, et al. Safety and efficacy of the SGLT2 inhibitor dapagliflozin in older patients with type 2 diabetes. Diabetologia. 2013;56((Fioretto P.) University of Padova Medical School, Italy):S383.
Meeting abstract

Fitzpatrick L, Kravitz B, Northcutt A, et al. The effects of rosiglitazone on bone by multiple image modalities in postmenopausal women with type 2 diabetes mellitus. Osteoporosis International. 2011;22((Fitzpatrick L.) GlaxosmithKline Pharmaceuticals, Research and Development, Biopharm R and D, Upper Merion, United States):S111-S2.
Meeting abstract

Fitzpatrick LA, Nino AJ, Kravitz B, et al. Understanding the effects of rosiglitazone on bone as measured by DXA and HSA: A mechanistic study in postmenopausal women with type 2 diabetes mellitus. Journal of Bone and Mineral Research. 2010;25((Fitzpatrick L.A.) Biopharm R and D, GlaxosmithKline, United States):S239.
Meeting abstract

Fleck P, Inzucchi S, Seufert J, et al. Initial therapy with combination alogliptin plus pioglitazone in type 2 diabetes patients inadequately controlled with diet and exercise. Diabetologia. 2009;52(S1):S294.
Meeting abstract

Fleck P, Wilson C. Effect of alogliptin combined with pioglitazone on lipids and lipoprotein particles in patients with type 2 diabetes. Diabetes. 2012;61((Fleck P.; Wilson C.) Deerfield, United States):A300.
Meeting abstract

Fleck P, Wilson C. Effect of alogliptin in combination with pioglitazone on glycemic control by baseline A1C. Diabetes. 2012;61((Fleck P.; Wilson C.) Deerfield, United States):A295.
Meeting abstract

Flint A, Kapitza C, Hindsberger C, et al. The once-daily human glucagon-like peptide-1 (GLP-1) analog liraglutide improves postprandial glucose levels in type 2 diabetes patients. Adv Ther. 2011 Mar;28(3):213-26. PMID: 21340616.
Placebo-controlled trial; Follow-up less than 3 months

Fonseca V, Desouza C, Khan AN. Adding subcutaneous liraglutide to metformin reduces HbA1c more than adding oral sitagliptin in patients whose type 2 diabetes is poorly controlled with metformin alone. Evidence-Based Medicine. 2010;15(4):115-6.
No original data

Fonseca V, Gill J, Zhou R, et al. An analysis of early insulin glargine added to metformin with or without sulfonylurea: impact on glycaemic control and hypoglycaemia. Diabetes Obes Metab. 2011 Sep;13(9):814-22. PMID: 21481127.
No drug comparison of interest

Fonseca V, McDuffie R, Calles J, et al. Determinants of weight gain in the action to control cardiovascular risk in diabetes trial. Diabetes Care. 2013 Aug;36(8):2162-8. PMID: 23412077.
Does not apply

Fonseca V, Zhu T, Karyekar C, et al. Adding saxagliptin (SAXA) 5 mg is superior to uptitrating metformin extended release (MET XR) in type 2 diabetes mellitus (T2DM) patients with inadequate glycemic control on a stable dose of MET XR 1500 mg. Diabetes. 2011;60((Fonseca V.; Zhu T.; Karyekar C.; Hirshberg B.) New Orleans, United States):A279.
Meeting abstract

Forst T, Guthrie R, Goldenberg R, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. Diabetes Obes Metab. 2014 May;16(5):467-77. PMID: 24528605.
No drug comparison of interest

Forst T, Larbig M, Hohberg C, et al. Adding insulin glargine vs. NPH insulin to metformin results in a more efficient postprandial beta-cell protection in individuals with type 2 diabetes. Diabetes Obes Metab. 2010 May;12(5):437-41. PMID: 20415692.
No drug comparison of interest

Fragozo A, Puerta MF, Alfonso R, et al. Adherence to glimepiride for type 2 diabetics in Colombia. Value in Health. 2009;12(7):A507.
Meeting abstract

Franco DR, Baptista J, Abreu FRM, et al. Starting glargine in insulin-naive type 2 diabetic patients based on body mass index is safe. World Journal of Diabetes. 2014;5(1):69-75.
No drug comparison of interest

Franek E, Haluzik M, Canecki Varzic S, et al. IDegAsp provides superior FPG control and reduced hypoglycaemia vs BIAsp 30 in

insulin-naive adults with type 2 diabetes: A randomised phase 3 trial. Diabetologia. 2014;57(1):S380.
Meeting abstract

Franek E, Haluzik M, Canecki-Varzic S, et al. Insulin degludec/insulin aspart (IDegASP) provides superior FPG control and reduced hypoglycaemia vs. biphasic insulin aspart 30 (BIAsp 30) in insulin-naive adults with type 2 diabetes in a randomized phase 3 trial. Diabetes. 2014;63((Franek E.; Haluzik M.; Canecki-Varzic S.; Sargin M.; Macura S.; Zacho J.; Christiansen J.S.) Warsaw, Poland, Praha, Czech Republic, Osijek, Croatia, Istanbul, Turkey, Soborg, Denmark, Aarhus, Denmark):A225.
Meeting abstract

Frederich R, McNeill R, Berglind N, et al. The efficacy and safety of the dipeptidyl peptidase-4 inhibitor saxagliptin in treatment-naive patients with type 2 diabetes mellitus: a randomized controlled trial. Diabetol Metab Syndr. 2012;4(1):36. PMID: 22828124.
No drug comparison of interest

Frederich R, Ohman P, Berglind N, et al. Clinical characteristics and sustained glycaemic control: A 76-week, randomised, double-blind study of saxagliptin + metformin in treatment-naive patients with type 2 diabetes. Diabetologia. 2011;54((Frederich R.; Berglind N.; Allen E.) Bristol-Myers Squibb, Princeton, United States):S337-S8.
Meeting abstract

Frederich R, Parikh SJ, Allen E, et al. Early onset of increased hypoglycemic incidence with glipizide (GLIP) vs. saxagliptin (SAXA) in type 2 diabetes patients on metformin. Diabetes. 2013;62((Frederich R.; Parikh S.J.; Allen E.; Bryzinski B.; Cook W.; Hirshberg B.) Princeton, NJ, Wilmington, DE):A299-A300.
Meeting abstract

Freeman MK. Efficacy and safety of linagliptin (tradjenta) in adults with type-2 diabetes mellitus. P T. 2011 Dec;36(12):807-42. PMID: 22346314.
No original data

Fu AZ, Qiu Y, Davies MJ, et al. Initial sulfonylurea use and subsequent insulin therapy in older subjects with type 2 diabetes mellitus. Diabetes Ther. 2012 Nov;3(1):12. PMID: 23076984.
No drug comparison of interest

Fu AZ, Qiu Y, Davies MJ, et al. Risk of cardiovascular disease associated with sulfonylurea or metformin use in older patients with type 2 diabetes. Diabetes. 2011;60((Fu A.Z.; Qiu Y.; Davies M.J.; Engel S.S.) Cleveland, United States):A10.
Fu AZ, Qiu Y, Davies MJ, et al. Risk of cardiovascular disease associated with sulphonylurea or metformin use in older patients with type 2 diabetes mellitus. Diabetologia. 2011;54((Fu A.Z.) Cleveland Clinic, Cleveland, United States):S72.
Meeting abstract

Fu H, Curtis BH, Schuster D, et al. Treatment patterns among older patients with type 2 diabetes in the United States: A retrospective cohort study. Diabetes. 2013;62((Fu H.; Curtis B.H.; Schuster D.; Festa A.; Kendall D.M.) Indianapolis, IN, Vienna, Austria):A686.
Meeting abstract

Fu H, Xie W, Curtis B, et al. Identifying factors associated with hypoglycemia-related hospitalizations among elderly patients with T2DM in the US: a novel approach using influential variable analysis.

Curr Med Res Opin. 2014 May 29:1-7. PMID: 24810150.
Does not meet study design criteria; No drug comparison of interest

Fujimoto K, Hamamoto Y, Honjo S, et al. Pioglitazone increases the risk of diabetic macular oedema in patients with type 2 diabetes. Diabetologia. 2013;56((Fujimoto K.; Hamamoto Y.; Honjo S.; Tatsuoka H.; Matsuoka A.; Wada Y.; Ikeda H.; Koshiyama H.) Center for Diabetes and Endocrinology, Osaka, Japan):S28.
Meeting abstract

Fujimoto K, Hamamoto Y, Honjo S, et al. Possible link of pioglitazone with bladder cancer in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract. 2013 Feb;99(2):e21-3. PMID: 23228390.
Does not meet study design criteria; No drug comparison of interest; Background medications

Fujishima Y, Maeda N, Inoue K, et al. Efficacy of liraglutide, a glucagon-like peptide-1 (GLP-1) analogue, on body weight, eating behavior, and glycemic control, in Japanese obese type 2 diabetes. Cardiovasc Diabetol. 2012;11:107. PMID: 22973968.
No drug comparison of interest; Background medications

Fujiwara T, Yoshida M, Nakamura T, et al. Dipeptidyl peptidase-4 inhibitors are associated with improved left ventricular diastolic function after acute myocardial infarction in diabetic patients. Heart and Vessels. 2014((Fujiwara T.; Nakamura T.; Sakakura K.; Wada H.; Arao K.; Katayama T.; Funayama H.; Sugawara Y.; Mitsuhashi T.; Momomura S.-I., momoshin@omiya.jichi.ac.jp) Department of Cardiovascular Medicine, Saitama Medical Center, Jichi Medical University, Saitama, Saitama 330-8503, Japan).
No drug comparison of interest; Background medications; Comorbidity

Fumisawa Y, Funase Y, Yamashita K, et al. Systematic analysis of risk factors for coronary heart disease in Japanese patients with type 2 diabetes: a matched case-control study. J Atheroscler Thromb. 2012;19(10):918-23. PMID: 22863783.
Follow-up less than 3 months; No drug comparison of interest

Funch D, Gydesen H, Tornoe K, et al. A prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs. Diabetes, Obesity and Metabolism. 2014;16(3):273-5.
Does not meet study design criteria; No drug comparison of interest

Furui H. Comparison examination of the clinical efficacy of 3 DPP-4 inhibitors on type 2 diabetes mellitus treatment: Combination effect with SU drug. Therapeutic Research. 2013;34(7):985-9.
No drug comparison of interest

Furukawa K, Hanyu O, Heianza Y, et al. High-dose metformin vs. Sitagliptin in addition to metformin 750mg in insufficiently controlled japanese type 2 diabetes patients with metformin 750mg. Diabetes. 2013;62((Furukawa K.; Hanyu O.; Heianza Y.; Uemura Y.; Kawada R.; Yamamoto M.; Osawa T.; Kaneko M.; Yamada T.; Suzuki H.; Minagawa S.; Yamada A.; Suzuki A.; Sone H.) Niigata, Japan):A671.
Meeting abstract

Gada E, Owens AW, Gore MO, et al. Discordant effects of rosiglitazone on novel

inflammatory biomarkers. Am Heart J. 2013 Apr;165(4):609-14. PMID: 23537979.
Placebo-controlled trial; Background medications

Gallwitz B, Bohmer M, Segiet T, et al. Effects of exenatide vs. insulin aspart on glycaemic control and hypoglycaemia in patients with Type 2 diabetes treated with metformin: Primary results for the metformin arm of a 26-week, Randomised, Open-label study. Diabetic Medicine. 2011;28((Gallwitz B.) Department of Medicine IV, University Hospital of Tubingen, Tubingen, Germany):72.
Meeting abstract

Gallwitz B, Bohmer M, Segiet T, et al. Exenatide vs. insulin aspart in patients with type 2 diabetes: Results of a randomised, open-label s tudy. Diabetologia. 2010;53((Gallwitz B.) Department of Medicine IV, University Hospital Tubingen, Germany):S343.
Meeting abstract

Gallwitz B, Dotta F, Kazda C, et al. Changes in adipokines in type 2 diabetic patients treated with exenatide versus glimipiride on metformin background - Results of a prospective, randomized controlled study over 9 months. Diabetologia. 2009;52(S1):S313.
Meeting abstract

Gallwitz B, Kusterer K, Hildemann S. The therapy of type 2 diabetes in clinical practice - Results from a standardized non-interventional register (SIRTA). Diabetologie und Stoffwechsel. 2012;7(6):434-41.
Does not report long-term outcomes or adverse events; No outcome of interest

Gallwitz B, Rosenstock J, Emser A, et al. Linagliptin is more effective than glimepiride at achieving a composite outcome of A1C target with no hypoglycemia and no weight gain over 2 years in mildly hyperglycemic T2D pts on metformin. Diabetes. 2012;61((Gallwitz B.; Rosenstock J.; Emser A.; Von Eynatten M.; Woerle H.-J.) Tubingen, Germany):A268.
Meeting abstract

Gallwitz B, Rosenstock J, Emser A, et al. Linagliptin is more effective than glimepiride at achieving a composite outcome of target HbA(1)c < 7% with no hypoglycaemia and no weight gain over 2 years. Int J Clin Pract. 2013 Apr;67(4):317-21. PMID: 23521323.
No outcome of interest

Gallwitz B, Rosenstock J, Patel S, et al. Regardless of the degree of glycemic control, Linagliptin (LINA) has lower hypoglycemia risk than all doses of Glimepiride (GLIM), at all timeg points over a 2-year trial. Diabetologie und Stoffwechsel. 2014;9((Gallwitz B.) Universitatsklinikum Tubingen, Medizinische Klinik IV, Tubingen, Germany).
Meeting abstract

Gallwitz B, Uhlig-Laske B, Bhattacharaya S, et al. Linagliptin has similar efficacy to glimepiride but improved cardiovascular safety over 2 years in patients with type 2 diabetes inadequately controlled on metformin. Diabetes, Stoffwechsel und Herz. 2011;20(6):417-8.
Meeting abstract

Ganz ML, Xu Y, Wintfeld NS, et al. Rates and costs of severe hypoglycemic events in type 2 diabetes in the United States: Findings from a systematic literature review and electronic health records. Diabetes. 2013;62((Ganz M.L.; Xu Y.; Wintfeld N.S.; Li Q.; Lee Y.-C.; Byrnes M.J.; Ashaye A.O.;

Gatt E.; Huang J.C.) Lexington, MA, Princeton, NJ):A407.
Meeting abstract

Garber A, Falahati A, Toft AD. Meta-analysis of the effect of liraglutide, a once-daily human GLP-1 analogue, on lipids and markers of cardiovascular risk in type 2 diabetes. Diabetic Medicine. 2010;27(2):157.
Meeting abstract

Garber A, Henry R, Ratner R, et al. Liraglutide, a human GLP-1 analogue, offers sustained and greater reduction in HbA1c, fasting plasma glucose and weight compared with glimepiride over 2 years, with lower hypoglycaemic risk, in patients with Type 2 diabetes: LEAD-3 extension study. Diabetic Medicine. 2010;27(2):78.
Meeting abstract

Garber A, Henry R, Ratner R, et al. Significantly better glycaemic control and weight reduction with liraglutide, a once-daily human GLP-1 analogue, compared with glimepiride: All as monotherapy in type 2 diabetes. Journal of Diabetes. 2009;1((Garber A.) Baylor College of Medicine, Houston, United States):A63.
Meeting abstract

Garber A, Henry R, Ratner RE, et al. Two years of treatment with liraglutide, a human GLP-1 analogue, offers sustained and greater reduction with HbA1c, FPG, PPG and weight compared with glimepiride, with lower glycaemic risk, in patients with type 2 diabetes: LEAD-3 extension study. Canadian Journal of Diabetes. 2009;33(3):289.
Meeting abstract

Garber A, Matthews D, Holst JJ, et al. The effect of diabetes duration on the response to liraglutide and glimepiride in type 2 diabetes. Journal of Diabetes. 2011;3((Garber A.) Baylor College of Medicine, Houston, United States):14-5.
Meeting abstract

Garber A, Thomsen A, Falahati A, et al. Liraglutide treatment provides greater weight loss with improved glycaemic control than sitagliptin, both combined with metformin. Diabetologia. 2010;53((Garber A.) Baylor College of Medicine, Houston, United States):S332.
Meeting abstract

Garber AJ, Henry R, Ratner R, et al. Liraglutide, a human GLP-1 analogue, maintains greater reductions in HbA1c, FPG and weight than glimepiride over 2 years in patients with type 2 diabetes: LEAD-3 extension study. Diabetologia. 2009;52(S1):S287-S8.
Meeting abstract

Garber AJ, Henry R, Ratner R, et al. Monotherapy with liraglutide, a once-daily human GLP-1 analog, provides sustained reductions in A1C, FPG, and weight compared with glimepiride in type 2 diabetes: LEAD-3 mono 2-year results. Diabetes. 2009;58((Garber A.J.; Henry R.; Ratner R.; Hale P.; Chang C.; Bode B.)).
Meeting abstract

Garcia-Garcia HM, Garg S, Brugaletta S, et al. Evaluation of in-stent restenosis in the APPROACH trial (Assessment on the Prevention of Progression by Rosiglitazone On Atherosclerosis in diabetes patients with Cardiovascular History). Int J Cardiovasc Imaging. 2012 Mar;28(3):455-65. PMID: 21359834.
Background medications

Garcia-Garcia HM, Serruys PW, Gerstein HC, et al. Serial assessments of coronary remodeling from the approach trial

(assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history). European Heart Journal. 2009;30((Garcia-Garcia H.M.; Serruys P.W.) Erasmus MC - Thoraxcenter, Rotterdam, Netherlands):298.
Meeting abstract

Garcia-Hernandez P, Arechavaleta-Granell Mdel R, Yamamoto J, et al. [Liraglutide and glimepiride on glycaemic control in type 2 diabetes in the Mexican cohort (LEAD 3)]. Rev Med Inst Mex Seguro Soc. 2010 Sep-Oct;48(5):543-8. PMID: 21205505.
Background medications; No drug comparison of interest

Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. Diabetes Care. 2010 Nov;33(11):2349-54. PMID: 20682680.
Does not account for confounding; Background medications

Garofolo M, Pucci L, Lucchesi D, et al. Effects of pioglitazone vs glyburide on endothelial function in type 2 diabetic patients with vascular complications: The SPLENDOR study. Diabetologia. 2013;56((Garofolo M.; Lucchesi D.; Russo E.; Sancho Bornez V.; Giusti L.; Dardano A.; Miccoli R.; Penno G.; Del Prato S.) Endocrinology and Metabolism, University of Pisa, Pisa, Italy):S392.
Meeting abstract

Garrett CR, Hassabo HM, Bhadkamkar NA, et al. Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. Br J Cancer. 2012 Apr 10;106(8):1374-8. PMID: 22421948.
No drug comparison of interest; Comorbidity

Gastaldelli A, Brodows RG, D'Alessio D. The effect of chronic twice daily exenatide treatment on beta-cell function in new onset type 2 diabetes. Clin Endocrinol (Oxf). 2014 Apr;80(4):545-53. PMID: 23574529.
Placebo-controlled trial; No outcome of interest; Background medications

Gatbonton P, Ko-De los Santos G, Domingo F, et al. Effectiveness and tolerability of vildagliptin versus other oral antidiabetic drugs in patients with type 2 diabetes mellitus in the Philippines: Results from one year observational study (EDGE). Phillippine Journal of Internal Medicine. 2013;51(4).
No drug comparison of interest

Gause-Nilsson I, De Bruin TW, Sugg JE, et al. Two-year efficacy and safety of dapagliflozin for T2DM patients with a history of cardiovascular disease. Diabetes. 2014;63((Gause-Nilsson I.; De Bruin T.W.; Sugg J.E.; Parikh S.J.; Johnsson E.; Leiter L.A.) Molndal, Sweden, Wilmington, DE, Toronto, ON, Canada):A271.
Meeting abstract

Gavin IJR, Davies MJ, Davies M, et al. Consistent effects of canagliflozin (CANA) across racial subgroups of patients with type 2 diabetes mellitus (T2DM). Diabetes. 2014;63((Gavin III J.R.; Davies M.J.; Davies M.; Vijapurkar U.; Alba M.; Meininger G.) Atlanta, GA, Leicester, United Kingdom, Raritan, NJ):A285.
Meeting abstract

Geiger MJ, Skrivanek Z, Gaydos B, et al. An adaptive, dose-finding, seamless phase 2/3 study of a long-acting glucagon-like peptide-1 analog (dulaglutide): trial design and baseline characteristics. J Diabetes Sci

Technol. 2012;6(6):1319-27. PMID: 23294776.
No original data

Gejl M, Starup-Linde J, Scheel-Thomsen J, et al. Diabetes treatment and composite endpoint: A nested case-control study. Diabetes. 2014;63((Gejl M.; Starup-Linde J.; Scheel-Thomsen J.; Gregersen S.; Vestergaard P.) Aarhus, Denmark, Aalborg, Denmark):A632.
Meeting abstract

Gejl M, Starup-Linde J, Scheel-Thomsen J, et al. Risk of cardiovascular disease events: The impact of diabetes and anti-diabetic drugs: A nested case-control study. Diabetologia. 2014;57(1):S101.
Meeting abstract

Geraldine N, Marc A, Carla T, et al. Relation between diabetes, metformin treatment and the occurrence of malignancies in a Belgian primary care setting. Diabetes Res Clin Pract. 2012 Aug;97(2):331-6. PMID: 22386769.
No drug comparison of interest

Gerstein HC, Ratner RE, Cannon CP, et al. Effect of rosiglitazone on progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary artery disease: the assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history trial. Circulation. 2010 Mar 16;121(10):1176-87. PMID: 20194881.
Background medications

Ghotbi AA, Kober L, Finer N, et al. Association of hypoglycemic treatment regimens with cardiovascular outcomes in overweight and obese subjects with type 2 diabetes: a substudy of the SCOUT trial. Diabetes Care. 2013 Nov;36(11):3746-53. PMID: 24089540.
Does not meet study design criteria

Gianturco V, Gianturco L, Bodini BD, et al. Long term effects of therapy with DPP-4 Inhibitors on fitness, cardiovascular function and mortality: A cohort study in elder population. European Heart Journal. 2014;35((Gianturco V.) Sapienza University of Rome, Department of Cardiov. and Respiratory Sciences, Nephrology and Geriatrics, Rome, Italy):1073.
Meeting abstract

Gilbert RE, Weir M, Januszewicz A, et al. Lower blood pressure (BP) with canagliflozin (CANA) in subjects with type 2 diabetes mellitus (T2DM). Canadian Journal of Diabetes. 2013;37((Gilbert R.E.; Weir M.; Januszewicz A.; Gonzalez F.L.; Meininger G.) Toronto, ON CAN; Baltimore, MD USA; Warsaw, Poland; Monterrey, Mexico; Raritan, NJ USA):S3.
Meeting abstract

Gilbert RE, Weir MR, Fioretto P, et al. Effect of canagliflozin (CANA) in patients with type 2 diabetes mellitus (T2DM) based on age and estimated glomerular filtration rate (EGFR). Diabetes. 2014;63((Gilbert R.E.; Weir M.R.; Fioretto P.; Law G.; Usiskin K.; Meininger G.) Toronto, ON, Canada, Baltimore, MD, Padova, Italy, Raritan, NJ):A267.
Meeting abstract

Giles TD, Elkayam U, Bhattacharya M, et al. Comparison of pioglitazone vs glyburide in early heart failure: insights from a randomized controlled study of patients with type 2 diabetes and mild cardiac disease. Congest Heart Fail. 2010 May-Jun;16(3):111-7. PMID: 20557330.
Background medications

Gill A, Hoogwerf BJ, Burger J, et al. Effect of exenatide on heart rate and blood pressure in subjects with type 2 diabetes mellitus: a double-blind, placebo-controlled, randomized pilot study. Cardiovasc Diabetol. 2010;9:6. PMID: 20109208.
No drug comparison of interest; Placebo-controlled trial

Giorda CB, Picariello R, Nada E, et al. Incretin therapies and risk of hospital admission for acute pancreatitis in an unselected population of European patients with type 2 diabetes: a case-control study. Lancet Diabetes Endocrinol. 2014 Feb;2(2):111-5. PMID: 24622714.
No drug comparison of interest

Gitt AK, Bramlage P, Binz C, et al. [Comorbidity, hypoglycaemia and appropriate selection of antidiabetic pharmacotherapy in diabetic patients with heart failure in clinical practice in Germany. Results of the DiaRegis registry]. Herz. 2012 May;37(3):294-300. PMID: 22476616
No drug comparison of interest; Background medications

Gitt AK, Bramlage P, Binz C, et al. Clinical impact on target achievement and complications of intensified glucose control on top of metformin: Sulfonylurea and insulin vs. incretin-based treatment in clinical practice. European Heart Journal. 2013;34((Gitt A.K.; Schneider S.) Institute of Myocardial Infarction Research, University of Heidelberg, Ludwigshafen, Germany):785.
Meeting abstract

Gitt AK, Bramlage P, Binz C, et al. Hypoglycaemia is more frequent in type 2 diabetic patients with co-morbid vascular disease: an analysis of the DiaRegis registry. Eur J Prev Cardiol. 2012 Aug;19(4):765-72. PMID: 21628353.
Does not account for confounding; Background medications

Gitt AK, Bramlage P, Binz C, et al. Outcome of sulfonylurea and insulin versus incretin-based treatment in type 2 diabetes patients uncontrolled on prior metformin mono therapy: Results of diaregis. Journal of the American College of Cardiology. 2014;63(12):A1336.
Meeting abstract

Gitt AK, Bramlage P, Deeg E, et al. Higher incidence of hypoglycaemia under oral anti-diabetic therapy in patients with type 2 diabetes and manifest vascular disease: 12-months follow-up of DiaRegis. European Heart Journal. 2012;33((Gitt A.K.) Herzzentrum Ludwigshafen, Institut f. Herzinfarktforschung Ludwigshafen, Univ. Heidelberg, Ludwigshafen am Rhein, Germany):889.
Meeting abstract

Gitt AK, Bramlage P, Deeg E, et al. Higher incidence of hypoglycaemia under oral anti-diabetic therapy in patients with type 2 diabetes and manifest vascular disease: Results of DiaRegis. European Heart Journal. 2011;32((Gitt A.K.) Herzzentrum Ludwigshafen, Institut f. Herzinfarktforschung Ludwigshafen, Univ. Heidelberg, Ludwigshafen am Rhein, Germany):974.
Meeting abstract

Gitt AK, Bramlage P, Schneider S, et al. Incidence and impact of hypoglycemia in diabetic patients with intensified glycaemic control in clinical practice-results of DiaRegis. European Heart Journal. 2014;35((Gitt A.K.) Herzzentrum Ludwigshafen + Institut f. Herzinfarktforschung Ludwigshafen, Ludwigshafen, Germany):1020-1.
Meeting abstract

Gitt AK, Bramlage P, Schneider S, et al. Outcome of sulfonylurea and insulin vs. Incretin-based treatment in type 2 diabetes patients uncontrolled on prior metformin mono therapy-results of DiaRegis. European Heart Journal. 2014;35((Gitt A.K.) Herzzentrum Ludwigshafen, Institut F. Herzinfarktforschung Ludwigshafen, Ludwigshafen, Germany):1073-4.
Meeting abstract

Gitt AK, Bramlage P, Schneider S, et al. Performance of DPP-4-inhhibitors versus sulfonylureas on top of metformin in a real world setting - Results of 2 years FU of DiaRegis. European Heart Journal. 2013;34((Gitt A.K.) Herzzentrum Ludwigshafen, Med. Klinik B, Kardiologie + Institut f. Herzinfarktforschung Ludwigshafen, Ludwigshafen am Rhein, Germany):1110-1.
Meeting abstract

Glass LC, Triplitt C, Lewis MS, et al. Effects of exenatide plus rosiglitazone on measures of beta cell function and insulin sensitivity in subjects with type 2 diabetes previously treated with metformin. Diabetologia. 2009;52(S1):S286.
Meeting abstract

Goke B, Gallwitz B, Eriksson J, et al. Saxagliptin vs glipizide as add-on therapy to metformin for type 2 diabetes mellitus (T2DM): Long-term safety and efficacy. Diabetes. 2011;60((Goke B.; Gallwitz B.; Eriksson J.; Bokelundsingh S.; Gause-Nilsson I.) Munich, Germany):A305.
Meeting abstract

Gokhale M, Funk MJ, Wyss R, et al. Comparative evaluation of short-term risk of cardiovascular events with antidiabetic step-up therapies among older adults. Pharmacoepidemiology and Drug Safety. 2012;21((Gokhale M.; Funk M.J.; Wyss R.; Pate V.; Sturmer T.) Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, United States):236-7.
Meeting abstract

Goldstein BJ, Seck T, Chen Y, et al. Sitagliptin compared with glimepiride provides similar efficacy with weight loss and less hypoglycaemia when added to metformin therapy in patients with type 2 diabetes mellitus. Diabetologia. 2010;53((Goldstein B.J.; Seck T.; Chen Y.; Duran L.; Johnson-Levonas A.O.; Kaufman K.D.; Williams-Herman D.E.) Merck Sharp and Dohme Corp., Rahway, United States):S325.
Meeting abstract

Gomez-Samano MA, Gulias-Herrero A, Cuevas-Ramos D, et al. Metformin and improvement of the hepatic insulin resistance index independent of anthropometric changes. Endocrine Practice. 2012;18(1):8-16.
No type 2 diabetes; No drug comparison of interest

Gomis R, Espadero RM, Jones R, et al. Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2011 Jul;13(7):653-61. PMID: 21410628.
No drug comparison of interst; Background medications

Gomis R, Owens DR, Taskinen MR, et al. Long-term safety and efficacy of linagliptin as monotherapy or in combination with other oral glucose-lowering agents in 2121 subjects with type 2 diabetes: up to 2 years exposure in 24-week phase III trials

followed by a 78-week open-label extension. Int J Clin Pract. 2012 Aug;66(8):731-40. PMID: 22691164.
Background medications; Does not meet study design criteria

Gonzalez-Galvez G, Jodar E, Kim K, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus who were, or were not, on antihyperglycaemic agents at screening. Diabetologia. 2014;57(1):S347-S8.
Meeting abstract

Gonzalez-Galvez G, Kim KA, Jodar E, et al. Effect of canagliflozin (CANA) in patients with type 2 diabetes mellitus (T2DM) who were, or were not, on antihyperglycemic agents (AHAS) at screening. Diabetes. 2014;63((Gonzalez-Galvez G.; Kim K.-A.; Jodar E.; Alba M.; Tong C.; Meininger G.) Guadalajara, Mexico, Goyang-si, Republic of Korea, Madrid, Spain, Raritan, NJ):A280.
Meeting abstract

Gonzalez-Perez A, Schlienger RG, Garcia Rodriguez LA. Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: A population-based cohort study. Diabetes Care. 2010;33(12):2580-5.
No drug comparison of interest

Gosmanova EO, Canada RB, Wan J, et al. Different antidiabetic regimens and the development of renal dysfunction in US Veterans with type 2 diabetes mellitus. J Investig Med. 2012 Oct;60(7):1009-14. PMID: 22801248.
No drug comparison of interest

Gough S, Zinman B, Falahati A, et al. The proportion of patients reaching the composite outcome of HbA1c <7.0%, no hypoglycaemia and no weight gain with different Type 2 diabetes therapies in the Liraglutide Effect and Action in Diabetes (LEAD) programme. Diabetic Medicine. 2010;27(2):77.
Meeting abstract

Gough SC, Zinman B, Brett J, et al. Achievement of glycaemic control and weight loss with liraglutide, exenatide and sitagliptin. Diabetic Medicine. 2012;29((Gough S.C.) OCDEM, National Institute for Health Research (NIHR), Oxford Biomedical Research Centre, University of Oxford, Oxford, United Kingdom):69.
Meeting abstract

Grabner M, Wei W, Raparla S, et al. Real-world comparative effectiveness analysis of patients initiating injectable treatments for type 2 diabetes mellitus (T2DM): Pilot data from the initiator study. Value in Health. 2012;15(7):A494.
Meeting abstract

Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA. 2010 Jul 28;304(4):411-8. PMID: 20584880.
Background medications

Grandy S, Fox KM, Hardy E. Association of Weight Loss and Medication Adherence Among Adults With Type 2 Diabetes Mellitus: SHIELD (Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes). Curr Ther Res Clin Exp. 2013 Dec;75:77-82. PMID: 24465048.
No drug comparison of interest; Does not meet study design criteria

Grandy S, Hashemi M, Langkilde AM, et al. Changes in weight loss-related quality of life among type 2 diabetes mellitus patients

treated with dapagliflozin. Diabetes Obes Metab. 2014 Jul;16(7):645-50. PMID: 24443876.
No outcome of interest

Grandy S, Ingelganullrd A, Langkilde A, et al. Weight loss-related quality of life among type 2 diabetes mellitus (T2DM) patients treated with dapagliflozin. Diabetes. 2013;62((Grandy S.; Ingelganullrd A.; Langkilde A.; Sugg J.E.; Parikh S.J.) Wilmington, DE, Molndal, Sweden):A667-A8.
Meeting abstract

Grandy S, Ingelgard A, Sjostrom CD, et al. Treatment with dapagliflozin over 52 weeks maintains health-related quality of life in high cardiovascular risk patients with type 2 diabetes mellitus. Circulation: Cardiovascular Quality and Outcomes. 2013;6(3).
Meeting abstract

Grandy S, Langkilde AM, Ingelganullrd A, et al. Quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin for 24 weeks. Diabetes. 2012;61((Grandy S.; Langkilde A.-M.; Ingelganullrd A.; Sugg J.E.; Parikh S.J.) Wilmington, United States):A600.
Meeting abstract

Grandy S, Langkilde AM, Sugg JE, et al. Health-related quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin over 2 years. Int J Clin Pract. 2014 Apr;68(4):486-94. PMID: 24499168.
No outcome of interest

Greco D, Pisciotta M, Gambina F, et al. Severe hypoglycaemia leading to hospital admission in type 2 diabetic patients aged 80 years or older. Exp Clin Endocrinol Diabetes. 2010 Apr;118(4):215-9. PMID: 20072965.
Does not account for confounding

Grey A, Beckley V, Doyle A, et al. Pioglitazone increases bone marrow fat in type 2 diabetes: results from a randomized controlled trial. Eur J Endocrinol. 2012 Jun;166(6):1087-91. PMID: 22408124.
Does not apply; Placebo-controlled trial

Grey A, Bolland M, Fenwick S, et al. The skeletal effects of pioglitazone in type 2 diabetes or impaired glucose tolerance: a randomized controlled trial. Eur J Endocrinol. 2014 Feb;170(2):255-62. PMID: 24217934.
Placebo-controlled trial; No type 2 diabetes

Grimm M, Han J, Weaver C, et al. Efficacy, safety, and tolerability of exenatide once weekly in patients with type 2 diabetes mellitus: an integrated analysis of the DURATION trials. Postgrad Med. 2013 May;125(3):47-57. PMID: 23748506.
No drug comparison of interest

Groop PH, Cooper M, Perkovic V, et al. Effects of the DPP-4 inhibitor linagliptin on albuminuria in patients with type 2 diabetes and diabetic nephropathy. Diabetologia. 2012;55((Groop P.-H.) Department of Medicine, Helsinki University, Central Hospital, Finland):S20-S1.
Meeting abstract

Groop PH, Cooper M, Perkovic V, et al. Linagliptin lowers albuminuria on top of recommended standard treatment for diabetic nephropathy. Diabetes. 2012;61((Groop P.-H.; Cooper M.; Perkovic V.; Emser A.; Von Eynatten M.; Woerle H.-J.) Helsinki, Finland):A243.
Meeting abstract

Groop PH, Cooper ME, Perkovic V, et al. Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. Diabetes Care. 2013 Nov;36(11):3460-8. PMID: 24026560.
Background medications; Placebo-controlled trial

Groop PH, Del Prato S, Taskinen MR, et al. Linagliptin treatment in subjects with type 2 diabetes with and without mild-to-moderate renal impairment. Diabetes Obes Metab. 2014 Jun;16(6):560-8. PMID: 24612167.
Background medications

Groop PH, Laakso M, Rosenstock J, et al. Linagliptin versus placebo followed by glimepiride in type 2 diabetes patients with moderate to severe renal impairment. Diabetologia. 2013;56((Groop P.-H.) Helsinki University Central Hospital, Department of Medicine, Division of Nephrology, Helsinki, Finland):S364-S5.
Meeting abstract

Groop PH, Perkovic V, Cooper M, et al. Long-term efficacy and safety of linagliptin in type 2 diabetes patients with moderate to severe renal disease. Diabetes. 2014;63((Groop P.-H.; Perkovic V.; Cooper M.; Crowe S.; Lee J.; Patel S.; Von Eynatten M.) Helsinki, Finland, Sydney, Australia, Melbourne, Australia, Ingelheim, Germany, Bracknell, United Kingdom, Ridgefield, CT):A264.
Meeting abstract

Groop PH, Von Eynatten M, Emser A, et al. Efficacy and safety of linagliptin in type 2 diabetes patients at high risk of renal complications: Results from a large phase 3 program. Diabetes. 2011;60((Groop P.-H.; Von Eynatten M.; Emser A.; Patel S.; Woerle H.J.) Helsinki, Finland):A605.
Meeting abstract

Gross P. Influence of pioglitazone for renal transplant function in diabetics - a double blind randomised placebo controlled cross over study. clinicaltrials.gov/ct2/show/NCT00507494; 2011.
No original data

Grunberger G, Chang A, Garcia Soria G, et al. Monotherapy with the once-weekly GLP-1 analogue dulaglutide for 12 weeks in patients with Type 2 diabetes: dose-dependent effects on glycaemic control in a randomized, double-blind, placebo-controlled study. Diabet Med. 2012 Oct;29(10):1260-7. PMID: 22804250.
Placebo-controlled trial

Grunberger G, Chang A, Soria MGG, et al. Monotherapy with the once weekly long-acting GLP-1 analog LY2189265 for 12 weeks in patients with type 2 diabetes: Dose-dependent effects on glycemic control in a randomized, double-blind, placebo-controlled study. Diabetes. 2011;60((Grunberger G.; Chang A.; Soria M.G.G.; Botros F.T.; Bsharat R.; Milicevic Z.) Bloomfield Hills, United States):A300.
Meeting abstract

Gruntmanis U, Fordan S, Ghayee HK, et al. The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone increases bone resorption in women with type 2 diabetes: a randomized, controlled trial. Calcif Tissue Int. 2010 May;86(5):343-9. PMID: 20354684.
Placebo-controlled trial; Background medications

Gudipaty L, Rosenfeld NK, Fuller CS, et al. Effect of Exenatide, Sitagliptin, or Glimepiride on beta-Cell Secretory Capacity in Early Type 2 Diabetes. Diabetes Care. 2014 Jun 26PMID: 24969577.

No type 2 diabetes

Guerci B, Weinstock R, Umpierrez G, et al. Safety and efficacy of dulaglutide versus sitagliptin after 104 weeks in type 2 diabetes (award-5). Canadian Journal of Diabetes. 2013;37((Guerci B.; Weinstock R.; Umpierrez G.; Nauck M.; Boleyn K.; Skrivanek Z.; Milicevic Z.) Vandoeuvre les Nancy, France; Syracuse, NY USA; Atlanta, GA USA; Bad Lauterberg, Germany; Indianapolis, IN USA; Vienna, Austria):S44-S5.
Meeting abstract

Guerci B, Weinstock RS, Umpierrez G, et al. Safety and efficacy of dulaglutide vs sitagliptin after 104 weeks in type 2 diabetes (AWARD-5). Diabetologia. 2013;56((Guerci B.) Diabetology, Metabolic Diseases and Nutrition and CIC Inserm ILCV, University of Nancy i, Vandoeuvre les Nancy, France):S367-S8.
Meeting abstract

Guo M, Mi J, Jiang QM, et al. Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. Clin Exp Pharmacol Physiol. 2014 May 24PMID: 24862430.
No drug comparison of interest; Placebo-controlled trial

Gupta AK, Bray GA, Greenway FL, et al. Pioglitazone, but not metformin, reduces liver fat in Type-2 diabetes mellitus independent of weight changes. J Diabetes Complications. 2010 Sep-Oct;24(5):289-96. PMID: 19577936.
Background medications

Gupta M, Teoh H, Kajil M, et al. The effects of rosiglitazone on inflammatory biomarkers and adipokines in diabetic, hypertensive patients. Exp Clin Cardiol. 2012 Winter;17(4):191-6. PMID: 23592934.
Background medications; No drug comparison of interest

Gurieva I, Pfuetzner A, Antsiferov M, et al. Saxagliptin improves glycaemic control either as add-on therapy to metformin or as initial combination therapy with metformin in patients with type 2 diabetes. European Heart Journal. 2009;30((Gurieva I.) Federal Bureau of Medicine and Social Expertise, Moscow, Russian Federation):226-7.
Meeting abstract

Gusmao G, Moureira M, Sosa F. Combination with linagliptin improves the tolerability of metformin in type 2 diabetic patients previously labelled as intolerant to metformin. Diabetologia. 2014;57(1):S366.
Meeting abstract

Haak T, Meinicke T, Jones R, et al. Combination of linagliptin and metformin improves glycemic control in type 2 diabetes: A randomized trial with an open-label arm in patients with poor glycemic control. Diabetes. 2011;60((Haak T.; Meinicke T.; Jones R.; Von Eynatten M.; Woerle H.J.) Bad Mergentheim, Germany):A77.
Meeting abstract

Habib ZA, Havstad SL, Wells K, et al. Thiazolidinedione use and the longitudinal risk of fractures in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2010 Feb;95(2):592-600. PMID: 20061432.
Background medications

Habib ZA, Tzogias L, Havstad SL, et al. Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: A time-updated propensity analysis.

Pharmacoepidemiology and Drug Safety. 2009;18(6):437-47.
No drug comparison of interest; Background medications

Hach T, Gerich J, Salsali A, et al. Empagliflozin improves glycaemic parameters and cardiovascular risk factors in patients with type 2 diabetes: Pooled data from four pivotal phase III trials. Diabetologia. 2013;56((Hach T.; Salsali A.; Kim G.; Woerle H.J.; Broedl U.C.) Boehringer Ingelheim, Germany):S377-S8.
Meeting abstract

Hach T, Gerich J, Salsali A, et al. Empagliflozin improves glycaemic parameters and cardiovascular risk factors in patients with type 2 diabetes: Pooled data from four pivotal phase III trials. Giornale Italiano di Cardiologia. 2014;15(4):e55.
Meeting abstract

Hach T, Gerich J, Salsali A, et al. Empagliflozin improves glycaemic parameters and cardiovascular risk factors in patients with Type 2 diabetes: Pooled data from four randomised, placebo-controlled phase III trials. Diabetic Medicine. 2014;31((Hach T.; Salsali A.; Kim G.; Woerle H.J.; Broedl U.C.) Boehringer Ingelheim Pharma GmbH and Co. KG, Ingelheim, Germany):64-5.
Meeting abstract

Hach T, Gerich J, Salsali A, et al. Empagliflozin improves glycemic parameters and cardiovascular risk factors in patients with Type 2 Diabetes (T2DM): Pooled data from four pivotal phase III trials. Diabetologie und Stoffwechsel. 2014;9((Hach T.; Salsali A.; Kim G.; Woerle H.J.; Broedl U.C.) Boehringer Ingelheim Pharma GmbH and Co. KG, Ingelheim, Germany).
Meeting abstract

Hach T, Lambers Heerspink HJ, Pfarr E, et al. The sodium glucose cotransporter-2 (SGLT-2) inhibitor empagliflozin lowers blood pressure independent of weight or HbA1c changes. Diabetologia. 2012;55((Hach T.; Pfarr E.; Lund S.; Ley L.; Broedl U.C.; Woerle H.J.) Boehringer Ingelheim Pharma GmbH and Co. KG, Ingelheim, Germany):S317.
Meeting abstract

Hage C, Brismar K, Lundman P, et al. The DPP-4 inhibitor sitagliptin and endothelial function in patients with acute coronary syndromes and newly detected glucose perturbations: A report from the BEGAMI study. Diab Vasc Dis Res. 2014 May 19;11(4):290-3. PMID: 24845072.
No type 2 diabetes; No drug comparison of interest; Placebo-controlled trial

Halimi S, Aubert JP, Fontbonne A, et al. A real-life study of the use, effectiveness and tolerability of rosiglitazone in France: the AVANCE study. Diabetes Metab. 2012 Oct;38(4):343-51. PMID: 22521038.
No drug comparison of interest

Hammar N, Farahmand B, Andersson S, et al. Incidence of urinary tract infection in subjects with type 2 diabetes. Experience from adverse event reporting in diabetes clinical trials. Pharmacoepidemiology and Drug Safety (PDS). 2009;18(S1):S41-S2.
Meeting abstract

Hammar N, Farahmand B, Gran M, et al. Incidence of urinary tract infection in patients with type 2 diabetes. Experience from adverse event reporting in clinical trials. Pharmacoepidemiology and Drug Safety. 2010;19(12):1287-92.
Does not apply; Background medications

Hanefeld M, Fleischmann H, Landgraf W, et al. EARLY study: Early basal insulin therapy under real-life conditions in type 2 diabetics. Diabetes, Stoffwechsel und Herz. 2012;21(2):91-7.
No drug comparison of interest

Hanefeld M, Kleine I, Fuchs W, et al. Comparison of pioglitazone vs metformin and effects of the combina tion of both on cardiovascular risk factors in type 2 diabetes with stable insulin therapy: The PIOCOMB study. Diabetes. 2011;60((Hanefeld M.; Kleine I.; Fuchs W.; Pfutzner A.; Forst T.) Dresden, Germany):A317-A8.
Meeting abstract

Hansen L, Zee P, Li Y, et al. Randomised, double-blind trial of dual add-on saxagliptin plus dapagliflozin vs saxagliptin or dapagliflozin add-on alone in poorly controlled type 2 diabetes on metformin. Diabetologia. 2014;57(1):S8.
Meeting abstract

Haque AF, Haque MZ, Ekram AS, et al. Comparison between effect of glimepiride and pioglitazone on the C-reactive protein level of type 2 diabetic patient. Journal of Medicine. 2011;12(1):30-3.
Does not meet study design criteria; Not outcome of interest

Hardy E, Ptaszynska A, De Bruin TWA, et al. Dapagliflozin effects on the lipid profile of patients with type 2 diabetes mellitus. Diabetes. 2013;62((Hardy E.; Ptaszynska A.; De Bruin T.W.A.; Johnsson E.; Parikh S.J.; List J.F.) Wilmington, DE, Princeton, NJ):A310.
Meeting abstract

Hardy E, Rohwedder K, Hrub V, et al. Dapagliflozin, a selective SGLT2 inhibitor, reduces serum levels of uric acid in patients with type 2 diabetes. Diabetologia. 2011;54((Hardy E.; Sugg J.; Parikh S.) AstraZeneca, Wilmington, United States):S344-S5.
Meeting abstract

Hardy E, Salsali A, Hruba V, et al. Efficacy increases with increasing baseline HbA1c category with dapagliflozin therapy. Diabetes. 2012;61((Hardy E.; Salsali A.; Hruba V.; Mansfield T.; Rohwedder K.; Wessman C.; Sugg J.; Wei L.; Ptaszynska A.; Parikh S.) Wilmington, United States):A23.
Meeting abstract

Haring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin for 24 weeks improves glycemic control in patients with type 2 diabetes (T2DM). Diabetes. 2013;62((Haring H.-U.; Merker L.; Seewaldt-Becker E.; Weimer M.; Meinicke T.; Broedl U.C.; Woerle H.J.) Tubingen, Germany, Dormagen, Germany, Biberach, Germany, Ingelheim, Germany):A282.
Meeting abstract

Haring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2013;36(11):3396-404.
No drug comparison of interest

Haring HU, Merker L, Seewaldt-Becker E, et al. Improved glycaemic control with empagliflozin as add-on to metformin in a 24-week phase III trial in patients with Type 2 diabetes (EMPA-REG MET(trademark)). Diabetic Medicine. 2014;31((Haring H.U.) University of Tubingen, Tubingen, Germany):66.
Meeting abstract

Harris S, Sinclair A, Bode B, et al. Efficacy and safety of canagliflozin (CANA) in older subjects with type 2 diabetes mellitus (T2DM). Canadian Journal of Diabetes. 2013;37((Harris S.; Sinclair A.; Bode B.; Vijapurkar U.; Gassmann-Mayer C.; Fung A.; Shaw W.; Usiskin K.; Desai M.; Meininger G.) London, ON CAN; Luton, UK; Atlanta, GA USA; Titusville, NJ USA):S25-S6.
Meeting abstract

Hassabo HM, Hassan M, George B, et al. Survival advantage associated with metformin usage in patients with colorectal cancer (CRC) and type II noninsulin-dependent diabetes (NIDDM). Journal of Clinical Oncology. 2011;29(15).
Meeting abstract

Hassan MM, Curley SA, Li D, et al. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer. 2010;116(8):1938-46.
Background medications; No drug comparison of interest

He X, Esteva FJ, Ensor J, et al. Metformin and thiazolidinediones are associated with improved breast cancer-specific survival of diabetic women with HER2+ breast cancer. Ann Oncol. 2012 Jul;23(7):1771-80. PMID: 22112968.
No drug comparison; Comorbidity

He XX, Tu SM, Lee MH, et al. Thiazolidinediones and metformin associated with improved survival of diabetic prostate cancer patients. Ann Oncol. 2011 Dec;22(12):2640-5. PMID: 21415239.
No drug comparison of interest; Background medications; Comorbidity

Heggie AJ, Walker M. Renal function in patients with Type 2 diabetes treated with glucagon-like peptide 1 (GLP-1) analogues. Diabetic Medicine. 2013;30((Heggie A.J.; Walker M.) Newcastle Diabetes Centre, Newcastle General Hospital, Newcastle, United Kingdom):162-3.
Meeting abstract

Heise T, Mathieu C, Hey-Hadavi J, et al. Glycemic control with preprandial versus basal insulin in patients with type 2 diabetes mellitus poorly controlled by oral antidiabetes agents. Diabetes Technology and Therapeutics. 2010;12(2):135-41.
No an FDA-approved formulation; No drug comparison of interest

Heller S, Adetunji O, Tahbaz A, et al. Patient-reported outcomes in a trial of exenatide once weekly vs insulin detemir in patients with Type 2 diabetes treated with metformin alone or with sulphonylurea. Diabetic Medicine. 2013;30((Heller S.) Academic Unit of Diabetes, Endocrinology and Metabolism, University of Sheffield, Sheffield, United Kingdom):58.
Meeting abstract

Henriksen K, Byrjalsen I, Qvist P, et al. Efficacy and safety of the partial PPAR{gamma} agonist balaglitazone compared with pioglitazone and placebo: A Phase III, randomized, parallel-group study in patients with type 2 diabetes on stable insulin therapy. Endocrine Reviews. 2011;32(3).
Meeting abstract

Henry R, Buse J, Sesti G, et al. Efficacy of anthiyperglycemic therapies and the influence of baseline hemoglobin A1C: A meta-analysis of the liraglutide development program. Endocrine Practice. 2011;17(6):906-13.
Background medications; No original data

Henry RR, Buse JB, Sesti G, et al. Efficacy of antihyperglycemic therapies and the influence of baseline hemoglobin A(1C): a meta-analysis of the liraglutide development program. Endocr Pract. 2011 Nov-Dec;17(6):906-13. PMID: 22193143.
Handsearch

Henry RR, Murray AV, Herrera Marmolejo M, et al. Dapagliflozin, Metformin-XR, or both together to initiate pharmacologic therapy for type 2 diabetes. Diabetologia. 2011;54((Henry R.R.) University of California, San Diego School of Medicine, San Diego, United States):S67.
Meeting abstract

Henry RR, Smith SR, Schwartz SL, et al. Effects of saxagliptin on beta-cell stimulation and insulin secretion in patients with type 2 diabetes. Diabetes Obes Metab. 2011 Sep;13(9):850-8. PMID: 21554520.
Placebo-controlled trial

Hense HW, Kajueter H, Wellmann J, et al. Cancer incidence in a cohort of type 2 diabetics. American Journal of Epidemiology. 2011;173((Hense H.W.; Kajueter H.; Wellmann J.; Batzer U.; Heidinger O.) Cancer Registry NRW and University Muenster, Muenster, Germany):S235.
Meeting abstract

Hense HW, Kajuter H, Wellmann J, et al. Cancer incidence in type 2 diabetes patients - first results from a feasibility study of the D2C cohort. Diabetol Metab Syndr. 2011;3(1):15. PMID: 21752291.
No drug comparison of interest; Background medications

Henson K, Hight R, Welborn D, et al. Initial therapy for type 2 diabetes. Examination of a combination approach. Adv Nurse Pract. 2009 Jun;17(6):43-4. PMID: 20000183.
No original data

Hermans MP, Delibasi T, Farmer I, et al. Effects of saxagliptin added to sub-maximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: Results from the PROMPT study. Diabetologia. 2011;54((Hermans M.P.) Cliniques Universitaires Saint-Luc, Brussels, Belgium):S337.
Meeting abstract

Hermansen K, Kolotkin RL, Hammer M, et al. Patient-reported outcomes in patients with type 2 diabetes treated with liraglutide or glimepiride, both as add-on to metformin. Prim Care Diabetes. 2010 Jul;4(2):113-7. PMID: 20444662.
No outcome of interest

Hess G, Kaltheuner M, Scheper N, et al. Characteristics of 833 patients newly treated with GLP-1 analogs or DPP-IV inhibitors in 38 diabetes specialized medical practices in Germany. Diabetes. 2011;60((Hess G.; Kaltheuner M.; Scheper N.; Von Hubbenet J.; Hess E.; Faber-Heinemann G.; Krakow D.; Lederle M.; Molinski M.; Nitzsche G.; Reuter H.-M.; Simonsohn M.; Heinemann L.) Dusseldorf, Germany):A598.
Meeting abstract

Hess G. Clinical outcome of treatment with DPP-4-inhibitors or GLP-1-analogues in patients with type 2 diabetes treated in diabetes specialised medical practices in Germany. Diabetologia. 2012;55((Hess G.) WinDiab, Dusseldorf, Germany):S353.
Meeting abstract

Hibuse T, Maeda N, Kishida K, et al. A pilot three-month sitagliptin treatment increases serum adiponectin level in Japanese patients with type 2 diabetes mellitus--a randomized controlled trial START-J study. Cardiovasc Diabetol. 2014;13:96. PMID: 24884787.

Background medications; No drug comparison of interest

Hirshberg B, Bryzinski B, Xu J, et al. Efficacy and safety of saxagliptin as monotherapy in patients with type 2 diabetes: A pooled analysis. Diabetes. 2014;63((Hirshberg B.; Bryzinski B.; Xu J.; Monyak J.; Iqbal N.) Wilmington, DE, Princeton, NJ):A610.
Meeting abstract

Hirshberg B, Fonseca V, Minervini G, et al. Saxagliptin vs uptitrated metformin extended release: Effect of baseline HbA1c on efficacy and safety. Endocrine Reviews. 2012;33(3).
Meeting abstract

Hirshberg B, Parker A, Edelberg H, et al. Safety of saxagliptin: events of special interest in 9156 patients with type 2 diabetes mellitus. Diabetes Metab Res Rev. 2013 Dec 3PMID: 24376173.
Background medications

Hisada M, Munsaka M, Streit J, et al. An integrated, multi study analysis of alogliptin safety. Diabetologia. 2012;55((Hisada M.; Munsaka M.; Streit J.; Smith N.) Takeda Global Research and Development Center, Inc., Deerfield, United States):S347.
Meeting abstract

Hitron A, Adams V, Talbert J, et al. The influence of antidiabetic medications on the development and progression of prostate cancer. Cancer Epidemiol. 2012 Aug;36(4):e243-50. PMID: 22417708.
No drug comparison of interest

Hohberg C, Larbig M, Pfutzner A, et al. (beta)-cell-relieving effects of basal insulin plus metformin (MET) treatment in type 2 diabetes (T2D) patients (Pts) using insulin glargine (GLA) or NPH insulin (NPH). Diabetes. 2009;58((Hohberg C.; Larbig M.; Pfutzner A.; Roth W.; Forst T.)).
Meeting abstract

Holman R. DRN251 (TECOS). A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control. 2009.
No original data

Hong SJ, Kim JS, Park JH, et al. Three-year cardiovascular event rates were lower in type 2 diabetic patients with pioglitazone treatment after zotarolimus-eluting stent implantation. Journal of the American College of Cardiology. 2011;58(20):B26.
Meeting abstract

Honjo S, Kawasaki Y, Hamamoto Y, et al. Incidence and type of cancer in Japanese subjects with type 2 diabetes. Diabetologia. 2011;54((Honjo S.; Kawasaki Y.; Hamamoto Y.; Mori K.; Wada Y.; Ikeda H.; Nomura K.; Koshiyama H.) Center for Diabetes and Endocrinology, Tazuke Kofukai Medical Research Institute, Osaka, Japan):S311-S2.
Meeting abstract

Horne L, Ming EE, Karyekar C, et al. Saxagliptin in combination with metformin allows more patients to reach a composite end point of HbA1c <7% without weight gain or hypoglycemia. Diabetes. 2011;60((Horne L.; Ming E.E.; Karyekar C.; Donovan M.; Frederich R.; Ravichandran S.) Wilmington, United States):A620.
Meeting abstract

Horowitz M, Flint A, Jones KL, et al. Effect of the once-daily human GLP-1 analogue liraglutide on appetite, energy intake, energy expenditure and gastric emptying in type 2

diabetes. Diabetes Res Clin Pract. 2012 Aug;97(2):258-66. PMID: 22446097.
Follow-up less than 3 months

Horsdal HT, Mehnert F, Rungby J, et al. Type of preadmission antidiabetic treatment and outcome among patients with ischemic stroke: a nationwide follow-up study. J Stroke Cerebrovasc Dis. 2012 Nov;21(8):717-25. PMID: 21536457.
Comorbidity

Horton E, Taylor K, Booker Porter T, et al. Once-weekly exenatide used for six months provided improved glycaemic control and weight loss compared with sitagliptin, pioglitazone or insulin glargine in metformin-treated patients with Type 2 diabetes. Diabetic Medicine. 2011;28((Horton E.) Joslin Diabetes Center, Boston, United States):70-1.
Meeting abstract

Horton ES, Silberman C, Davis KL, et al. Weight loss and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies in a large cohort database. Diabetes. 2009;58((Horton E.S.; Silberman C.; Davis K.L.; Berria R.)).
Does not report long-term outcomes or adverse events

Horton ES, Silberman C, Davis KL, et al. Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort database. Diabetes Care. 2010 Aug;33(8):1759-65. PMID: 20460445.
Does not meet study design criteria; Bakground medications

Hsia SH. Insulin glargine compared to NPH among insulin-naive, U.S. inner city, ethnic minority type 2 diabetic patients. Diabetes Research and Clinical Practice. 2011;91(3):293-9.
No drug comparison of interest; Background medications

Hsiao FY, Mullins CD, Huang WF. Economic evaluation of thiazolidinediones as add-on therapy for treatment of type 2 diabetic patients in the Taiwanese national health insurance system. Value in Health. 2010;13(7):A507.
Meeting abstract

Hsiao FY. Does cardiovascular risk decrease after discontinuing rosiglitazone use? Early and late effects of rosiglitazone on the risk of myocardial infarction in type 2 diabetic patients. Drug Information Journal. 2009;43(4):521.
Meeting abstract

Hsieh MC, Lee TC, Cheng SM, et al. The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the Taiwanese. Exp Diabetes Res. 2012;2012:413782. PMID: 22719752.
Does not account for confounding

Hsu CC, Wahlqvist ML, Lee MS, et al. Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. J Alzheimers Dis. 2011;24(3):485-93. PMID: 21297276.
No outcome of interest

Hsu YHE, Yang YT, Chen PN, et al. Association between pioglitazone and bladder cancer among patients with type II diabetes: A propensity score matched cohort study. Value in Health. 2014;17(3):A73.
Meeting abstract

Hu M, Luo Y, Zhang L, et al. [Comparison on efficacy and safety of two regimens for treatment of type 2 diabetes mellitus: glargine plus metformin versus neutral

protamine hagedorn plus metformin]. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi. 2010 Jun;27(3):622-5. PMID: 20649032.
Non-English language

Hu Y, Li L, Xu Y, et al. Short-term intensive therapy in newly diagnosed type 2 diabetes partially restores both insulin sensitivity and (beta)-cell function in subjects with long-term remission. Diabetes Care. 2011;34(8):1848-53.
No drug comparison of interest

Hu YY, Ye SD, Zhao LL, et al. Hydrochloride pioglitazone decreases urinary cytokines excretion in type 2 diabetes. Clin Endocrinol (Oxf). 2010 Dec;73(6):739-43. PMID: 20874769.
Background medications

Hu YY, Ye SD, Zhao LL, et al. Hydrochloride pioglitazone decreases urinary TGF-beta1 excretion in type 2 diabetics. Eur J Clin Invest. 2010 Jul;40(7):571-4. PMID: 20482594.
Background medications

Huang ES, Karter AJ, Danielson KK, et al. The association between the number of prescription medications and incident falls in a multi-ethnic population of adult type-2 diabetes patients: The diabetes and aging study. Journal of General Internal Medicine. 2010;25(2):141-6.
No outcome of interest; No drug comparison of interest

Huang ES, Laiteerapong N, Liu JY, et al. Rates of complications and mortality in older patients with diabetes mellitus : the diabetes and aging study. JAMA Internal Medicine. 2014;174(2):251-8.
No drug comparison of interest

Hughes AD, Park C, March K, et al. A randomized placebo controlled double blind crossover study of pioglitazone on left ventricular diastolic function in type 2 diabetes. Int J Cardiol. 2013 Aug 20;167(4):1329-32. PMID: 22525343.
No drug comparison of interest

Hughes AD, Park CM, Khir AW, et al. Pioglitazone treatment improves left ventricular function in type 2 diabetics. Circulation. 2011;124(21).
Meeting abstract

Huskinson AC, Bottomley MJ, Clapham L, et al. A 5 year study of severe treatment-induced hypoglycaemia in diabetes: Patient characteristics and first year mortality. Diabetologia. 2012;55((Huskinson A.C.; Bottomley M.J.; Alzahrani S.H.; King R.; Ajjan R.A.) Multidisciplinary Cardiovascular Research Centre, Leeds Institution of Genetics, Health and Therapeutics, University of Leeds, Leeds, United Kingdom):S253.
Meeting abstract

Idorn T, Knop FK, Jorgensen MB, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes and end-stage renal disease: An investigator-initiated, randomised, placebocontrolled trial. Diabetologia. 2014;57(1):S370-S1.
Meeting abstract

Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. Arch Intern Med. 2012 Jul 9;172(13):1005-11. PMID: 22688528.
No drug comparison of interest; Background medications

Igata S, Tahara N, Tahara A, et al. Visceral fat metabolic activity is independently associated with coronary artery inflammation in patients with impaired glucose intolerance or type 2 diabetes.

Circulation. 2014;130((Igata S.; Tahara N.; Tahara A.; Nitta Y.; Honda A.; Kodama N.; Mizoguchi M.; Yamagishi S.-I.; Fukumoto Y.) Medicine, Div of Cardio-Vascular Medicine, Kurume Univ, Kurume, Japan).
Meeting abstract

Ikeda H, Ida K, Usami M, et al. Efficacy and safety of low-dose sitagliptin (25 mg) in elderly ((greater-than or equal to)70 years old) Japanese patients with type 2 diabetes. Diabetologia. 2013;56((Ikeda H.; Ida K.; Usami M.; Ikeda M.) Seimeikai Ikeda Hospital, Amagasaki-City, Japan):S370.
Meeting abstract

Inagaki N, Atsumi Y, Oura T, et al. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. Clin Ther. 2012 Sep;34(9):1892-908 e1. PMID: 22884767.
Background medications; No drug comparison of interest

Inagaki N, Kondo K, Iwasaki T, et al. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2 (SGLT2) improves glycemic control and reduces body weight in Japanese type 2 diabetes mellitus (T2DM). Diabetes. 2011;60((Inagaki N.; Kondo K.; Iwasaki T.; Maruyama N.; Susuta Y.; Sakai M.; Kuki H.) Kyoto, Japan):A274.
Meeting abstract

Inagaki N, Kondo K, Yoshinari T, et al. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes Obes Metab. 2013 Dec;15(12):1136-45. PMID: 23782594.
Placebo-controlled trial; No drug comparison of interest

Inagaki N, Watada H, Murai M, et al. Linagliptin added to sulphonylurea or (alpha)-glucosidase inhibitor therapy provides similar long-term safety and efficacy to metformin in Japanese patients with type 2 diabetes. Diabetologia. 2012;55((Inagaki N.) Department of Diabetes and Clinical Nutrition, Kyoto University, Graduate School of Medicine, Kyoto, Japan):S350.
Meeting abstract

Inagaki N, Watada H, Murai M, et al. Linagliptin provides effective, well-tolerated add-on therapy to pre-existing oral antidiabetic therapy over 1 year in Japanese patients with type 2 diabetes. Diabetes Obes Metab. 2013 Sep;15(9):833-43. PMID: 23565760.
No drug comparison of interest

Ingelganullrd A, Grandy S, Langkilde A, et al. Health-related quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin for 24 weeks. Diabetologia. 2012;55((Ingelganullrd A.; Langkilde A.) AstraZeneca, Molndal, Sweden):S320.
Meeting abstract

Inzucchi SE, Rosenstock J, Seufert J, et al. Effect of combination therapy with alogliptin and pioglitazone in drug-naive patients with type 2 diabetes on (beta)-cell function and insulin resistance. Diabetes. 2009;58((Inzucchi S.E.; Rosenstock J.; Seufert J.; Fleck P.; Wilson C.; Mekki Q.)).
Meeting abstract

Ioacara S, Guja C, Ionescu-Tirgoviste C, et al. Glucose lowering treatment and cancer specific mortality in type 2 diabetes. Diabetes. 2012;61((Ioacara S.; Guja C.;

Ionescu-Tirgoviste C.; Sabau S.; Fica S.; Tiu C.) Bucharest, Romania):A378.
Meeting abstract

Ioacara S, Roden M, Guja C, et al. Cardiovascular safety of metformin and sulphonylureas in type 2 diabetes patients. Diabetologia. 2014;57(1):S318.
Meeting abstract

Ionova TI, Nikitina TP, Kurbatova KA, et al. Usefulness of the hypoglycemia perspectives questionnaire (HPQ) in management of patients with type 2 diabetes. Value in Health. 2013;16(7):A447.
Meeting abstract

Iqbal N, Allen E, Donovan M, et al. Saxagliptin monotherapy or combination therapy: Outcomes by duration of type 2 diabetes. Diabetes. 2012;61((Iqbal N.; Allen E.; Donovan M.; Ohman P.) Princeton, United States):A619-A20.
Meeting abstract

Iqbal N, Allen E, Ohman P. Long-term safety and tolerability of saxagliptin add-on therapy in older patients (aged >/= 65 years) with type 2 diabetes. Clin Interv Aging. 2014;9:1479-87. PMID: 25214775.
Background medications; Placebo-controlled trial

Iqbal N, Parker A, Frederich R, et al. Assessment of the cardiovascular safety of saxagliptin in patients with type 2 diabetes mellitus: pooled analysis of 20 clinical trials. Cardiovasc Diabetol. 2014;13:33. PMID: 24490835.
No drug comparison of interest; Background medications

Iqbal N, Weber MA, Mansfield TA, et al. Dapagliflozin lowered ambulatory BP in patients with type 2 diabetes mellitus and hypertension inadequately controlled by a reninangiotensin system blocker (plus or minus) another agent. Diabetologia. 2014;57(1):S334.
Meeting abstract

Irace C, Fiorentino R, Carallo C, et al. Exenatide improves glycemic variability assessed by continuous glucose monitoring in subjects with type 2 diabetes. Diabetes Technol Ther. 2011 Dec;13(12):1261-3. PMID: 21751893.
Does not account for confounding; No outcome of interest

Ishikawa S, Shimano M, Watarai M, et al. Impact of Sitagliptin on Carotid Intima-Media Thickness in Patients With Coronary Artery Disease and Impaired Glucose Tolerance or Mild Diabetes Mellitus. Am J Cardiol. 2014 May 16PMID: 24929624.
No type 2 diabetes

Ito H, Abe M, Antoku S, et al. Comparison of the antidiabetic effects of linagliptin among groups with a normal renal function and a mild or severe renal impairment - retrospective observation study of Japanese patients with type 2 diabetes mellitus. Expert Opin Pharmacother. 2015 Feb;16(3):289-96. PMID: 25529857.
No drug comparison of interest

Iwamoto Y, Taniguchi T, Nonaka K, et al. Dose-ranging efficacy of sitagliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus. Endocr J. 2010;57(5):383-94. PMID: 20332588.
Background medications

Jabbour S, Hardy E, De Bruin TW, et al. Dapagliflozin helps reduce HbA1c and body weight in patients with type 2 diabetes as part of triple combination therapy: A subanalysis of four clinical studies. Diabetologia. 2013;56((Jabbour S.) Division

of Endocrinology,Diabetes and Metabolic Diseases, Jefferson Medical College of Thomas Jefferson University, Philadelphia, United States):S375.
Meeting abstract

Jaiswal M, Martin CL, Pop-Busui R. Effects of exenatide on measures of small fiber neuropathy in patients with type 2 diabetes. Diabetes. 2014;63((Jaiswal M.; Martin C.L.; Pop-Busui R.) Ann Arbor, United States):A149.
Meeting abstract

Janssen J, Van Den Berg E, Mattheus M, et al. Relationship between glycaemic control and cognitive function in patients with type 2 diabetes at elevated cardiovascular risk. Alzheimer's and Dementia. 2014;10((Janssen J., j.janssen-5@umcutrecht.nl) UMC Utrecht, Utrecht, Netherlands):P907-P8.
Meeting abstract

Jansson SP, Svardsudd K, Andersson DK. Effects of fasting blood glucose levels and blood pressure and treatment of diabetes and hypertension on the incidence of cardiovascular disease: a study of 740 patients with incident Type 2 diabetes with up to 30 years' follow-up. Diabet Med. 2014 Jun 3PMID: 24894815.
Background medications; Does not meet study design criteria

Januszewicz A, Lavalle Gonzalez F, Davidson J, et al. Efficacy and safety of Canagliflozin in subjects with type 2 diabetes mellitus on background metformin. Diabetologie und Stoffwechsel. 2013;8((Januszewicz A.) Department of Hypertension, Institute of Cardiology, Warsaw, Poland).
Meeting abstract

Jariwala K, Banahan BF, Yang Y, et al. Adherence and persistence among type II diabetic patients starting monotherapy on oral hypoglycemic agents. Value in Health. 2010;13(3):A62.
Meeting abstract

Jenkins-Jones S, Currie CJ, Mukherjee J, et al. Association between first-line monotherapy with sulfonylurea versus metformin and risk of all-cause mortality. Diabetologia. 2013;56((Jenkins-Jones S.) Global Epidemiology, Pharmatelligence, United Kingdom):S89.
Meeting abstract

Jensen TM, Saha K, Steinberg W. Assessment of acute pancreatitis in liraglutide type 2 diabetes trials. Pancreatology. 2013;13(2):e38.
Meeting abstract

Jensen TM, Saha K, Steinberg WM. Is There a Link Between Liraglutide and Pancreatitis? A Post Hoc Review of Pooled and Patient-Level Data From Completed Liraglutide Type 2 Diabetes Clinical Trials. Diabetes Care. 2014 Dec 12PMID: 25504028.
Does not account for confounding; No drug comparison of interest

Ji L, Han P, Liu Y, et al. Canagliflozin in Asian patients with type 2 diabetes on metformin alone or metformin in combination with sulphonylurea. Diabetes Obes Metab. 2015 Jan;17(1):23-31. PMID: 25175734.
No drug comparison of interest; Background medications

Ji L, Ma J, Li H, et al. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. Clin

Ther. 2014 Jan 1;36(1):84-100 e9. PMID: 24378206.
No drug comparison of interest; Placebo-controlled trial

Ji Q, Han P, Li C, et al. Efficacy and safety of alogliptin in subjects with type 2 diabetes: A randomised, double-blind, placebo-controlled, phase 3 study in mainland China, Taiwan and Hong Kong. Diabetologia. 2013;56((Ji Q.) First Affiliated Hospital of the Fourth Military Medical University, Xi'an, China):S365.
Meeting abstract

Jin P, Peng J, Zou H, et al. The 5-year onset and regression of diabetic retinopathy in Chinese type 2 diabetes patients. PLoS ONE. 2014;9(11).
Background medications; No drug comparison of interest

Johansen O, Neubacher D, Seck T, et al. Cardiovascular (CV) safety of linagliptin in patients with type 2 diabetes: A pooled comprehensive analysis of prospectively adjudicated CV events in phase 3 studies. Diabetologia. 2013;56((Johansen O.; Seck T.; Woerle H.-J.) Boehringer-Ingelheim, Ingelheim, Germany):S52.
Meeting abstract

Johansen OE, Neubacher D, Sech T, et al. Cardiovascular (CV) safety of linagliptin in patients with type 2 diabetes (T2D): A pooled comprehensive analysis of prospectively adjudicated CV events in phase 3 studies. Giornale Italiano di Cardiologia. 2014;15(4):e56.
Meeting abstract

Johansen OE, Neubacher D, Seck T, et al. Cardiovascular (CV) safety of linagliptin in patients with type 2 diabetes (T2D): A pooled comprehensive analysis of prospectively adjudicated CV events in phase 3 studies. Diabetes. 2013;62((Johansen O.E.; Neubacher D.; Seck T.; Patel S.; Woerle H.-J.) Ingelheim, Germany, Biberach, Germany, Bracknell, United Kingdom):A96.
Meeting abstract

Johansen OE, Neubacher D, Von Eynatten M, et al. Low cardiovascular (CV) risk hazard ratio observed with linagliptin in type 2 diabetes: Further insights from a predefined cv meta-analysis. Endocr Rev. 2012;33(3).
Meeting abstract

Johnson S, Ahren B, Stewart M, et al. HARMONY 3: 104 week efficacy of albiglutide compared to sitagliptin and glimepiride in patients with type 2 diabetes mellitus on metformin. Diabetologia. 2013;56((Johnson S.) GlaxoSmithKline, Research Triangle Park, United States):S8-S9.
Meeting abstract

Johnsson E, Johnsson KM, Mansfield TA, et al. Diuresis-related safety and tolerability of dapagliflozin in type 2 diabetes mellitus over 24 weeks. Diabetologia. 2014;57(1):S323.
Meeting abstract

Johnsson K, Ptaszynska A, Apanovitch A, et al. Safety of dapagliflozin in clinical trials for type 2 diabetes mellitus. Diabetologia. 2012;55((Johnsson K.) AstraZeneca, Molndal, Sweden):S304.
Meeting abstract

Johnsson KM, Ptaszynska A, Mansfield TA, et al. Dapagliflozin, a selective sodium-glucose cotransporter-2 inhibitor, does not increase risk of fractures. Diabetologia. 2014;57(1):S324-S5.
Meeting abstract

Johnston SS, Nguyen H, Felber E, et al. Retrospective study of adherence to glucagon-like peptide-1 receptor agonist therapy in patients with type 2 diabetes mellitus in the United States. Adv Ther. 2014 Nov;31(11):1119-33. PMID: 25408484.
No outcome of interest

Joly D, Choukroun G, Combe C, et al. Glycemic control according to glomerular filtration rate in patients with type 2 diabetes and overt nephropathy: A prospective observational study. Diabetes Res Clin Pract. 2015 Feb 12PMID: 25726333.
No drug comparison of interest

Jong GWT, Simon A, Valkhoff V, et al. Use of glucose lowering drugs and the risk of adenocarcinoma among patients with type 2 diabetes: A case-control study in the netherlands. Clinical Pharmacology and Therapeutics. 2013;93((Jong G.W.T.; Simon A.; Valkhoff V.; Sturkenboom M.) Erasmus University Rotterdam, Rotterdam, Netherlands):S92-S3.
Meeting abstract

Jonker JT, Lamb HJ, van der Meer RW, et al. Pioglitazone compared with metformin increases pericardial fat volume in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2010 Jan;95(1):456-60. PMID: 19915017.
No drug comparison of interest

Jonker JT, Meer RWVD, Rijzewijk LJ, et al. A differential effect of pioglitazone versus metformin on fat depots in patients with type 2 diabetes mellitus. Diabetes. 2009;58((Jonker J.T.; Meer R.W.V.D.; Rijzewijk L.J.; Menting L.J.; Diamant M.; Roos A.D.; Lamb H.J.; Smit J.W.A.; Romijn J.A.)).
Meeting abstract

Jorgensen CH, Gislason GH, Andersson C, et al. Effects of oral glucose-lowering drugs on long term outcomes in patients with diabetes mellitus following myocardial infarction not treated with emergent percutaneous coronary intervention--a retrospective nationwide cohort study. Cardiovasc Diabetol. 2010;9:54. PMID: 20843380.
Comorbidity

Jovanovic L, Peters AL, Jiang HH, et al. Durability of glycemic control with insulin lispro mix 75/25 versus insulin glargine for older patients with type 2 diabetes. Aging Clinical and Experimental Research. 2014;26(2):115-21.
No drug comparison of interest

Jun Hong S, Sang Kim J, Hyoung Park J, et al. Rates of cardiovascular events were lower in type 2 diabetic patients with pioglitazone treatment after zotarolimus-eluting stent implantation during the three-year follow-up. Circulation. 2011;124(21).
Meeting abstract

Juurlink DN, Gomes T, Lipscombe LL, et al. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. BMJ. 2009;339:b2942. PMID: 19690342.
Background medications

Kadowaki T, Haneda M, Inagaki N, et al. Empagliflozin monotherapy for 12 weeks improves glycemic control in Japanese patients with type 2 diabetes (T2DM). Diabetes. 2013;62((Kadowaki T.; Haneda M.; Inagaki N.; Taniguchi A.; Sakamoto M.; Koiwai K.; Rattunde H.; Woerle H.J.; Broedl U.C.) Tokyo, Japan, Asahikawa, Japan, Kyoto, Japan, Ingelheim, Germany):A297-A8.
Meeting abstract

Kadowaki T, Haneda M, Inagaki N, et al. Empagliflozin Monotherapy in Japanese Patients with Type 2 Diabetes Mellitus: a Randomized, 12-Week, Double-Blind, Placebo-Controlled, Phase II Trial. Adv Ther. 2014((Taniguchi A.; Koiwai K., kazuki.koiwai@boehringer-ingelheim.com) Clinical Development and Medical Affairs TA-Diabetes, Nippon Boehringer Ingelheim Co., Ltd., Tokyo, 141-6017, Japan).
Placebo-controlled trial

Kadowaki T, Namba M, Imaoka T, et al. Improved glycemic control and reduced bodyweight with exenatide: A double-blind, randomized, phase 3 study in Japanese patients with suboptimally controlled type 2 diabetes over 24 weeks. J Diabetes Investig. 2011 Jun 5;2(3):210-7. PMID: 24843486.
No drug comparison of interest; Background medications

Kahl S. Improvement of pancreatic (beta)-cell function in type 2 diabetes by treatment with liraglutide: The LIBRA Trial. Diabetologe. 2014;10(8):658-9.
Meeting abstract

Kahn SE, Haffner SM, Viberti G, et al. Rosiglitazone decreases C-reactive protein to a greater extent relative to glyburide and metformin over 4 years despite greater weight gain: observations from a Diabetes Outcome Progression Trial (ADOPT). Diabetes Care. 2010 Jan;33(1):177-83. PMID: 19808911.
No outcome of interest

Kahn SE, Lachin JM, Zinman B, et al. Effects of rosiglitazone, glyburide, and metformin on beta-cell function and insulin sensitivity in ADOPT. Diabetes. 2011 May;60(5):1552-60. PMID: 21415383.
No outcome of interest

Kaku K, Daida H, Kashiwagi A, et al. Long-term effects of pioglitazone in Japanese patients with type 2 diabetes without a recent history of macrovascular morbidity. Curr Med Res Opin. 2009 Dec;25(12):2925-32. PMID: 19835463.
No drug comparison of interest; Background medications

Kaku K, Inoue S, Matsuoka O, et al. Efficacy and safety of dapagliflozin as a monotherapy for type 2 diabetes mellitus in Japanese patients with inadequate glycaemic control: a phase II multicentre, randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab; 2013. p. 432-40.
Placebo-controlled trial

Kaku K, Kiyosue A, Inoue S, et al. Efficacy and safety of dapagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled with diet and exercise. Diabetes; 2013. p. A303.
Meeting abstract

Kalra S, Deepak MC, Narang P, et al. Correlation between measures of hypoglycemia and glycemic improvement in sulfonylurea treated patients with type 2 diabetes in India: results from the OBSTACLE hypoglycemia study. J Postgrad Med. 2014 Apr-Jun;60(2):151-5. PMID: 24823514.
No drug comparison of interest

Kalra S, Deepak MC, Narang P, et al. Usage pattern, glycemic improvement, hypoglycemia, and body mass index changes with sulfonylureas in real-life clinical practice: results from OBSTACLE Hypoglycemia Study. Diabetes Technol Ther. 2013 Feb;15(2):129-35. PMID: 23289432.
No drug comparison of interest

Kamoi K, Takeda K, Hashimoto K, et al. Identifying risk factors for clinically significant diabetic macula edema in patients with type 2 diabetes mellitus. Curr Diabetes Rev. 2013 May;9(3):209-17. PMID: 23363297.
Background medications

Kanada S, Koiwai K, Taniguchi A, et al. Pharmacokinetics, pharmacodynamics, safety and tolerability of 4 weeks' treatment with empagliflozin in Japanese patients with type 2 diabetes mellitus. J Diabetes Investig. 2013;4(6):613-7.
Placebo-controlled trial; Follow-up less than 3 months

Kanadiya MK, Gohel TD, Sanaka MR, et al. Relationship between type-2 diabetes and use of metformin with risk of colorectal adenoma in an American population receiving colonoscopy. J Diabetes Complications. 2013 Sep-Oct;27(5):463-6. PMID: 23755906.
No drug comparison of interest

Kanamori A, Matsuba I. Factors associated with reduced efficacy of sitagliptin therapy: analysis of 93 patients with type 2 diabetes treated for 1.5 years or longer. J Clin Med Res. 2013 Jun;5(3):217-21. PMID: 23671547.
Background medications; no drug comparison of interest

Kanazawa I, Yamaguchi T, Yamamoto M, et al. Relationship between treatments with insulin and oral hypoglycemic agents versus the presence of vertebral fractures in type 2 diabetes mellitus. J Bone Miner Metab. 2010 Sep;28(5):554-60. PMID: 20177722.
Background medications

Kanazawa I, Yamaguchi T, Yano S, et al. Baseline atherosclerosis parameter could assess the risk of bone loss during pioglitazone treatment in type 2 diabetes mellitus. Osteoporos Int. 2010 Dec;21(12):2013-8. PMID: 20130841.
Background medications

Kanazawa I, Yamamoto M, Yamaguchi T, et al. Effects of metformin and pioglitazone on serum pentosidine levels in type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2011 Jun;119(6):362-5. PMID: 21472665.
Background medications

Kao CH, Sun LM, Chen PC, et al. A population-based cohort study in Taiwan-use of insulin sensitizers can decrease cancer risk in diabetic patients? Annals of Oncology. 2013;24(2):523-30.
No drug comparison of interest

Karagianni P, Polyzos SA, Kartali N, et al. Comparative efficacy of exenatide versus insulin glargine on glycemic control in type 2 diabetes mellitus patients inadequately treated with metformin monotherapy. Adv Med Sci. 2013;58(1):38-43. PMID: 23640946.
Does not meet study design criteria

Karamanos B, Thanopoulou A, Drossinos V, et al. Study comparing the effect of pioglitazone in combination with either metformin or sulphonylureas on lipid profile and glycaemic control in patients with type 2 diabetes (ECLA). Curr Med Res Opin. 2011 Feb;27(2):303-13. PMID: 21142615.
Does not account for confounding

Kariadi SHKS. Hypoglycaemia and weight gain in diabetes management. Obesity Research and Clinical Practice. 2013;7((Kariadi S.H.K.S.) Division of Endocrinology and Metabolism, Department of Internal Medicine, Universitas Padjadjaran, Bandung, Indonesia):8.
Meeting abstract

Karl DM, Gill J, Zhou R, et al. Clinical predictors of risk of hypoglycaemia during addition and titration of insulin glargine for type 2 diabetes. Diabetologia. 2011;54((Karl D.M.) Endocrine Clinic, Portland, United States):S262-S3.
Meeting abstract

Karnieli E, Baeres FMM, Dzida G, et al. Observational study of once-daily insulin detemir in people with type 2 diabetes aged 75 years or older: A sub-analysis of data from the study of once-daily levemir (SOLVE). Drugs and Aging. 2013;30(3):167-75.
Does not apply

Karyekar C, Frederich R, Donovan M, et al. Achieving reductions in HbA1c (greater-than or equal to)1% without hypoglycemia with saxagliptin combination therapy: Post HOC analysis of 4 randomized controlled studies in patients with type 2 diabetes. Diabetes. 2011;60((Karyekar C.; Frederich R.; Donovan M.; Ravichandran S.) Princeton, United States):A594-A5.
Meeting abstract

Karyekar CS, Frederich R, Ravichandran S. Clinically relevant reductions in HbA1c without hypoglycaemia: results across four studies of saxagliptin. Int J Clin Pract. 2013 Aug;67(8):759-67. PMID: 23795975.
No outcome of interest

Karyekar CS, Ravichandran S, Allen E, et al. Tolerability and efficacy of glycemic control with saxagliptin in older patients (aged >/= 65 years) with inadequately controlled type 2 diabetes mellitus. Clin Interv Aging. 2013;8:419-30. PMID: 23626461.
Handsearch

Kashiwagi A, Kazuta K, Goto K, et al. Ipragliflozin in combination with metformin for the treatment of Japanese patients with type 2 diabetes: ILLUMINATE, a randomised, double-blind, placebo-controlled study. Diabetes Obes Metab. 2014 Jun 12PMID: 24919820.
No drug comparison of interest

Katz A, Ptaszynska A, Mansfield T, et al. Time course of changes in glycemic parameters and body weight in patients receiving dapagliflozin as add-on or as initial combination therapy with metformin. Diabetes. 2014;63((Katz A.; Ptaszynska A.; Mansfield T.; Iqbal N.; Sugg J.E.; Yeh H.; Parikh S.J.; List J.F.) Wilmington, DE, Princeton, NJ):A70.
Meeting abstract

Katz A, Yeh H, Sugg JE, et al. Efficacy of dapagliflozin in patients with type 2 diabetes mellitus and baseline HbA1c =9.0%. Diabetes. 2014;63((Katz A.; Yeh H.; Sugg J.E.; Parikh S.J.; List J.F.) Wilmington, DE, Princeton, NJ):A284-A5.
Meeting abstract

Kawaguchi T, Taniguchi E, Morita Y, et al. Association of exogenous insulin or sulphonylurea treatment with an increased incidence of hepatoma in patients with hepatitis C virus infection. Liver Int. 2010 Mar;30(3):479-86. PMID: 20040053.
Background medications; No drug comparison of interest

Kawamori R, Inagaki N, Araki E, et al. Linagliptin monotherapy provides superior glycaemic control versus placebo or voglibose with comparable safety in Japanese patients with type 2 diabetes: a randomized, placebo and active comparator-controlled, double-blind study. Diabetes Obes Metab. 2012 Apr;14(4):348-57. PMID: 22145698.

Placebo-controlled trial; Background medications

Kawamori R, Node K, Hanafusa T, et al. Baseline and 1-year interim follow-up assessment of Japanese patients initiating insulin therapy who were enrolled in the cardiovascular risk evaluation in people with type 2 diabetes on insulin therapy study: An international, multicenter, observational study. Cardiovascular Diabetology. 2013;12(1).
Background medications

Keoki Williams L, Padhukasahasram B, Ahmedani BK, et al. Differing Effects of Metformin on Glycemic Control by Race-Ethnicity. J Clin Endocrinol Metab. 2014 Jun 12:jc20141539. PMID: 24921653.
Does not meet study design criteria

Khalangot M, Kovtun V. Evaluation approach can significantly influence oral glucose-lowering drugs total mortality risks in retrospective cohorts of type 2 diabetes mellitus patients. Curr Diabetes Rev. 2014;10(5):336-42. PMID: 25336066.
Does not account for confounding; Background medications

Khimani F, Shah N, Curley BF, et al. Metformin use and renal cell cancer outcomes among patients with diabetes. Journal of Clinical Oncology. 2014;32(4).
Meeting abstract

Kim DL. Metformin based dual-combination therapies in drug naive type 2 diabetic patients. Diabetes Metab J. 2013 Dec;37(6):429-32. PMID: 24404514.
No original data

Kim G, Gerich J, Salsali A, et al. Urinary tract infections and genital infections in patients with Type 2 diabetes treated with empagliflozin: Pooled data from four randomised, placebo-controlled phase III trials. Diabetic Medicine. 2014;31((Kim G.; Salsali A.; Hach T.; Woerle H.J.; Broedl U.C.) Boehringer Ingelheim Pharma GmbH and Co. KG, Ingelheim, Germany):65.
Meeting abstract

Kim HS, Kim DM, Cha BS, et al. Efficacy of glimepiride/metformin fixed-dose combination versus metformin uptration in type 2 diabetic patients inadequately controlled on metformin monotherapy, a randomized, multicenter, parallel-group, open study in Korea. Diabetes. 2011;60((Kim H.-S.; Kim D.M.; Cha B.S.; Park T.S.; Kim K.; Kim D.-L.; Chung C.H.; Park J.H.; Jang H.C.; Choi D.-S.) Daegu, South Korea):A605.
Meeting abstract

Kim HS, Shin JA, Lee SH, et al. A comparative study of the effects of a dipeptidyl peptidase-IV inhibitor and sulfonylurea on glucose variability in patients with type 2 diabetes with inadequate glycemic control on metformin. Diabetes Technol Ther. 2013 Oct;15(10):810-6. PMID: 24050737.
Follow-up less than 3 months

Kim MK, Ko SH, Baek KH, et al. Long-term effects of rosiglitazone on the progressive decline in renal function in patients with type 2 diabetes. Korean J Intern Med. 2009 Sep;24(3):227-32. PMID: 19721859.
Does not meet study design criteria; Background medications

Kim SC, Glynn R, Liu J, et al. Dipeptidyl peptidase-4 inhibitors do not increase the risk of cardiovascular events in type 2 diabetes. Pharmacoepidemiology and Drug Safety. 2014;23((Kim S.C.; Glynn R.; Liu J.; Everett B.) Brigham and Women's Hospital, Boston, United States):188-9.

Control not specified; No drug comparison of interest

Kim SC, Schneeweiss S, Glynn RJ, et al. Dipeptidyl peptidase-4 inhibitors in type 2 diabetes may reduce the risk of autoimmune diseases. Arthritis and Rheumatism. 2013;65((Kim S.C.; Schneeweiss S.; Glynn R.J.; Doherty M.) Brigham and Women's Hospital, Boston, United States):S1133.
Meeting abstract

Kim SC, Schneeweiss S, Glynn RJ, et al. Dipeptidyl peptidase-4 inhibitors in type 2 diabetes may reduce the risk of autoimmune diseases: a population-based cohort study. Ann Rheum Dis. 2014 Jun 11PMID: 24919467.
Background medications; No outcome of interest

Kim WJ, Park CY, Jeong EH, et al. Retrospective analysis on the efficacy, safety and treatment failure group of sitagliptin for mean 10-month duration. Diabetes Metab J. 2011 Jun;35(3):290-7. PMID: 21785750.
No drug comparison of interest; Does not account for confounding

Kim YI, Kim SY, Cho SJ, et al. Long-term metformin use reduces gastric cancer risk in type 2 diabetics without insulin treatment: a nationwide cohort study. Aliment Pharmacol Ther. 2014 Apr;39(8):854-63. PMID: 24612291.
No drug comparison of interest

King AB, Montanya E, Pratley RE, et al. Liraglutide achieves A1C targets more often than sitagliptin or exenatide when added to metformin in patients with type 2 diabetes and a baseline A1C <8.0%. Endocr Pract. 2013 Jan-Feb;19(1):64-72. PMID: 23186975.
Handsearch

King DE, Player M, Everett CJ. The impact of pioglitazone on ADMA and oxidative stress markers in patients with type 2 diabetes. Prim Care Diabetes. 2012 Jul;6(2):157-61. PMID: 21705294.
Placebo-controlled trial; Background medications

Kirk JK, Davis SW, Lawrence K, et al. Outcomes and medication use in a longitudinal cohort of type 2 diabetes patients, 2006 to 2012. Journal of Clinical Outcomes Management. 2014;21(1):9-16.
Background medications

Klubo-Gwiezdzinska J, Costello Jr J, Patel A, et al. Treatment with metformin is associated with higher remission rate in diabetic patients with thyroid cancer. Journal of Clinical Endocrinology and Metabolism. 2013;98(8):3269-79.
Background medications; Comorbidity

Kodama N, Tahara N, Tahara A, et al. Effects of pioglitazone on visceral fat metabolic activity in impaired glucose tolerance or type 2 diabetes mellitus. J Clin Endocrinol Metab. 2013 Nov;98(11):4438-45. PMID: 24030946.
No type 2 diabetes; Background medications

Kodama N. Effects of pioglitazone versus glimepiride on abdominal fat glucose metabolism in patients with impaired glucose tolerance and/or type 2 diabetes mellitus. Circulation. 2012;126(21).
Meeting abstract

Kohan DE, Fioretto P, Tang W, et al. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic

control. Kidney Int. 2014 Apr;85(4):962-71. PMID: 24067431.
No drug comparison of interest; Placebo-controlled trial

Komajda M, McMurray JJ, Beck-Nielsen H, et al. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. Eur Heart J. 2010 Apr;31(7):824-31. PMID: 20118174.
Background medications

Kooy A, Jager JD, Lehert P, et al. Increase in value of adding metformin to insulin therapy in type 2 diabetes: More favorable weight with less macrovascular complications. Nederlands Tijdschrift voor Geneeskunde. 2009;153(21):1005-13.
Placebo-controlled trial

Koro CE, Sowell MO, Stender M, et al. The risk of acute pancreatitis with GLP-1 receptor agonists and DPP-4 inhibitors: A retrospective observational cohort study. Diabetologia. 2013;56((Koro C.E.) Worldwide Epidemiology, GlaxoSmithKline, Collegeville, United States):S183-S4.
Meeting abstract

Kos E, Liszek MJ, Emanuele MA, et al. Effect of metformin therapy on vitamin D and vitamin B(1)(2) levels in patients with type 2 diabetes mellitus. Endocr Pract. 2012 Mar-Apr;18(2):179-84. PMID: 21940283.
Does not apply; No outcome of interest

Kosi L, Chmelik M, Kautzky-Willer A. Impact of a DPP4-inhibitor on liver and heart lipid content and cardiovascular risk in type 2 diabetic patients. Diabetes. 2011;60((Kosi L.; Chmelik M.; Kautzky-Willer A.) Vienna, Austria):A609.
Meeting abstract

Kostev K, Dippel FW, Rathmann W. Glycemic control after initiating basal insulin therapy in patients with type 2 diabetes: a primary care database analysis. Diabetes Metab Syndr Obes. 2015;8:45-8. PMID: 25609990.
No drug comparison of interest; No outcome of interest

Kostev K, Dippel FW. Predictors for the initiation of a basal supported oral therapy (BOT) in type 2 diabetic patients under real-life conditions in Germany. Primary Care Diabetes. 2012;6(4):329-35.
Background medications

Kovacs CS, Seshiah V, Merker L, et al. Empagliflozin (EMPA) for (greater-than or equal to)76 weeks as add-on to pioglitazone with or without metformin in patients with type 2 diabetes (T2DM). Diabetes. 2014;63((Kovacs C.S.; Seshiah V.; Merker L.; Christiansen A.V.; Roux F.; Salsali A.; Kim G.; Stella P.; Woerle H.J.; Broedl U.C.) Newfoundland, NL, Canada, Chennai, India, Dormagen, Germany, Copenhagen, Denmark, Reims, France, Ingelheim, Germany):A273.
Meeting abstract

Kovacs CS, Seshiah V, Swallow R, et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: A 24-week, randomized, placebo-controlled trial. Diabetes, Obesity and Metabolism. 2014;16(2):147-58.
Background medications; No drug comparison of interest

Kowall B, Rathmann W, Kostev K. Are sulfonylurea and insulin therapies associated with a larger risk of cancer than metformin therapy? A retrospective database analysis.

Diabetes Care. 2015 Jan;38(1):59-65. PMID: 25336750.
Meeting abstract

Kozawa J, Kitamura T, Nishizawa H, et al. Dipeptidyl peptidase-4 inhibitors are effective in Japanese type 2 diabetic patients with sustained endogenous insulin-secreting capacity, a higher body mass index and insulin resistance. J Diabetes Investig. 2013;4(2):190-4.
Does not meet study design criteria

Krishnarajah G, Bhosle M, Chapman R. Patterns of up-titration in type 2 diabetes (T2DM) patients taking oral anti-diabetic drugs (OADs). Diabetes. 2009;58((Krishnarajah G.; Bhosle M.; Chapman R.)).
Meeting abstract

Krzymien J, Karnafel W. Lactic acidosis in patients with diabetes. Pol Arch Med Wewn. 2013;123(3):91-7. PMID: 23299861.
Kumar AA, Palamaner Subash Shantha G, Kahan S, et al. Intentional weight loss and dose reductions of anti-diabetic medications--a retrospective cohort study. PLoS One. 2012;7(2):e32395. PMID: 22384240.
No drug comparison of interest; Does not meet study design criteria

Kumar N, Kshitiz KK, Patra SK. Evaluation of role of oral anti-diabetic drugs on lipid profile in type 2 diabetes mellitus patients. International Journal of Pharma and Bio Sciences. 2010;1(4).
Does not meet study design criteria

Kunte H, Busch MA, Trostdorf K, et al. Hemorrhagic transformation of ischemic stroke in diabetics on sulfonylureas. Ann Neurol. 2012 Nov;72(5):799-806. PMID: 23280795.
No drug comparison of interest

Kuo CN, Lin YL, Wu MT. Cardiovascular risk associated with dipeptidyl peptidase-4 inhibitors compared with metformin. Pharmacotherapy. 2014;34(10):e294.
Meeting abstract

Kuribayashi N. Clinical study of insulin secretagogues in Japanese patients with type 2 diabetes: One-year comparison between the dipeptidyl peptidase 4 inhibitor sitagliptin and the sulfonylurea glimepiride. Therapeutic Research. 2013;34(4):521-30.
Non-English language

Kusama M, Nakashima E, Kouchi Y, et al. Long-term clinical efficacy and safety of GLP-1 analogue liraglutide vs. DPP-4 inhibitor sitagliptin in Japanese obese adults with type 2 diabetes. Journal of Diabetes. 2013;5((Kusama M.; Nakashima E.; Kouchi Y.; Imamine R.; Kawai M.; Watanabe M.; Sano T.; Hotta N.) Department of Diabetes and Endocrinology, Chubu Rosai Hospital, Nagoya, Japan):139.
Meeting abstract

Kusama M, Watarai A, Kawamura T, et al. The effects of DPP-4 inhibitor and postprandial hyperglycemia on vascular endothelial function in patients with type 2 diabetes mellitus. Diabetes. 2014;63((Kusama M.; Watarai A.; Kawamura T.; Kanai A.; Imamine R.; Kouchi Y.; Kawai M.; Minatoguchi M.; Mizoguchi A.; Nakashima E.; Hotta N.) Nagoya, Japan):A609.
Meeting abstract

Kutoh E, Ukai Y. Alogliptin as an initial therapy in patients with newly diagnosed, drug naive type 2 diabetes: a randomized, control trial. Endocrine. 2012 Jun;41(3):435-41. PMID: 22249941.
No drug comparison of interest

Laakso M, Rosenstock J, Groop PH, et al. Linagliptin vs. placebo followed by glimepiride in type 2 diabetes patients with moderate to severe renal impairment. Diabetes. 2013;62((Laakso M.; Rosenstock J.; Groop P.-H.; Hehnke U.; Tamminen I.; Patel S.; Von Eynatten M.; Woerle H.-J.) Kuopio, Finland, Dallas, TX, Helsinki, Finland, Ingelheim, Germany, Bracknell, United Kingdom):A281-A2.
Meeting abstract

Laakso M, Rosenstock J, Groop PH, et al. Treatmentwith the dipeptidyl peptidase-4 inhibitor linagliptin or placebo followed by glimepiride in patients with type 2 diabetes with moderate to severe renal impairment: A 52-week, randomized, double-blind clinical trial. Diabetes Care. 2015;38(2):e15-e7.
Background medications

Lachin JM, Viberti G, Zinman B, et al. Renal function in type 2 diabetes with rosiglitazone, metformin, and glyburide monotherapy. Clin J Am Soc Nephrol. 2011 May;6(5):1032-40. PMID: 21454723.
No outcome of interest

Lafata JE, Dobie EA, Divine GW, et al. Sustained hyperglycemia among patients with diabetes: what matters when action is needed? Diabetes Care. 2009 Aug;32(8):1447-52. PMID: 19638524.
No outcome of interest

Lai YC, Li HY, Wu TJ, et al. Correlation of Circulating Acid-Labile Subunit Levels with Insulin Sensitivity and Serum LDL Cholesterol in Patients with Type 2 Diabetes: Findings from a Prospective Study with Rosiglitazone. PPAR Res. 2014;2014:917823. PMID: 24966876.
No drug comparison of interest

Lajara R, Aguilar R, Hehnke U, et al. Efficacy and safety of linagliptin in subjects with long-standing type 2 diabetes mellitus (>10 years): evidence from pooled data of randomized, double-blind, placebo-controlled, phase III trials. Clin Ther. 2014 Nov 1;36(11):1595-605. PMID: 25236917.
Background medications; No drug comparison of interest

Lamberts EJF, Souverein PC, Hugtenburg JG, et al. Achieving glycemic control differs between patients with type 2 diabetes mellitus starting on metformin and sulfonylureas. Pharmacoepidemiology and Drug Safety. 2013;22((Lamberts E.J.F.; Souverein P.C.; Bouvy M.L.) Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands):184.
Meeting abstract

Landman GW, Kleefstra N, van Hateren KJ, et al. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes Care. 2010 Feb;33(2):322-6. PMID: 19918015.
Does not meet study design criteria; No drug comparison of interest

Langkilde A, Rohwedder K, Iqbal N, et al. Measures of beta cell function and insulin sensitivity over time in patients with type 2 diabetes receiving dapagliflozin versus glipizide as add-on therapy to metformin. Diabetologia. 2012;55((Langkilde A.) AstraZeneca, Molndal, Sweden):S308.
Meeting abstract

Langslet G, Cefalu WT, Leiter LA, et al. Canagliflozin demonstrates durable glycaemic improvements over 104 weeks compared with glimepiride in subjects with type 2 diabetes mellitus on metformin. Diabetologia. 2013;56((Langslet G.) Lipid Clinic, Oslo University Hospital, Norway):S81.

Meeting abstract

Langslet G, Davidson JA, Valentine V, et al. Canagliflozin reduces both HbA1c and body weight in patients with type 2 diabetes mellitus on background metformin. Diabetologia. 2014;57(1):S348.
Meeting abstract

Lavalle Gonzalez FJ, Januszewicz A, Davidson J, et al. Canagliflozin (CANA) compared with sitagliptin (SITA) in subjects with type 2 diabetes mellitus (T2DM) on metformin (MET) over 52 weeks. Diabetes. 2013;62((Lavalle Gonzalez F.J.; Januszewicz A.; Davidson J.; Qiu R.; Tong C.; Meininger G.) Monterrey, Mexico, Warsaw, Poland, Dallas, TX, Raritan, NJ):A61.
Meeting abstract

Lavalle-Gonzalez FJ, Chiquete E, de la Luz J, et al. Achievement of therapeutic targets in Mexican patients with diabetes mellitus. Endocrinol Nutr. 2012 Dec;59(10):591-8. PMID: 23137765.
No drug comparison of interest; Background medications

Lee BW. Efficacy and safety of biphasic insulin aspart 30/70 in type 2 diabetes suboptimally controlled on oral antidiabetic therapy in Korea: A multicenter, open-label, single-arm study (Diabetes Metab J 2013;37:117-24). Diabetes and Metabolism Journal. 2013;37(3):212-3.
No original data

Lee D, Han J, Brown C, et al. Safety and tolerability of exenatide once weekly pooled summary of 1095 patients from DURATION-1, 2 and 3. Diabetologie und Stoffwechsel. 2011;6((Lee D.; Han J.; Brown C.) Amylin, San Diego, United States).
Meeting abstract

Lee EY, Hwang S, Lee SH, et al. Postprandial C-peptide to glucose ratio as a predictor of (beta)-cell function and its usefulness for staged management of type 2 diabetes. Journal of Diabetes Investigation. 2014((Lee E.Y.; Hwang S.; Lee S.H.; Lee Y.-H.; Choi A.R.; Lee Y.; Lee B.-W.; Kang E.S.; Ahn C.W.; Cha B.S.; Lee H.C., endohclee@yuhs.ac) Department of Internal Medicine Yonsei University College of Medicine Seoul Korea).
No drug comparison of interest; No outcome of interest

Lee MS, Hsu CC, Wahlqvist ML, et al. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. BMC Cancer. 2011;11:20. PMID: 21241523.
No drug comparison of interest

Lee MY, Hsiao PJ, Yang YH, et al. The association of pioglitazone and urinary tract disease in type 2 diabetic Taiwanese: bladder cancer and chronic kidney disease. PLoS One. 2014;9(1):e85479. PMID: 24427312.
No drug comparison of interest; Background medications

Lee P, Chang A, Blaum C, et al. Comparison of safety and efficacy of insulin glargine and neutral protamine hagedorn insulin in older adults with type 2 diabetes mellitus: Results from a pooled analysis. Journal of the American Geriatrics Society. 2012;60(1):51-9.
No drug comparison of interest

Lee WC, Dekoven M, Bouchard J, et al. Improved real-world glycaemic outcomes with liraglutide versus other incretin-based

therapies in type 2 diabetes. Diabetes Obes Metab. 2014 Mar 1PMID: 24581276.
No drug comparison of interest

Lehrke M, Marx N, Patel S, et al. Safety and tolerability of linagliptin in 7400 patients with type 2 diabetes: A pooled comprehensive analysis of prospective safety reporting in placebo-controlled studies. Diabetologia. 2013;56((Lehrke M.; Marx N.) Department of Internal Medicine i, University Hospital Aachen, Germany):S395.
Meeting abstract

Lehrke M, Marx N, Patel S, et al. Safety and Tolerability of Linagliptin in Patients With Type 2 Diabetes: A Comprehensive Pooled Analysis of 22 Placebo-controlled Studies. Clin Ther. 2014 Aug 1;36(8):1130-46. PMID: 25015594.
No drug comparison of interest

Lehrke M. Corrections: Safety and tolerability of linagliptin in patients with type 2 diabetes: A comprehensive pooled analysis of 22 placebo-controlled studies (Clinical Therapeutics (2014) 36 (1130-1146)). Clinical Therapeutics. 2014;36(11):1705.
Meeting abstract

Leibovitz E, Gottlieb S, Goldenberg I, et al. Sitagliptin pretreatment in diabetes patients presenting with acute coronary syndrome: results from the Acute Coronary Syndrome Israeli Survey (ACSIS). Cardiovasc Diabetol. 2013;12:53. PMID: 23537430.
Background medications; Follow-up less than 3 months

Leiter L, Carr MC, Stewart M, et al. HARMONY 8: Once-weekly glucagon-like peptide 1 receptor agonist albiglutide vs sitagliptin for patients with type 2 diabetes with renal impairment: Week 26 results. Diabetologia. 2013;56((Leiter L.) University of Toronto, Canada):S361-S2.
Meeting abstract

Leiter L, Cefalu W, DeBruin T, et al. Dapagliflozin treatment for type 2 diabetes mellitus patients with a history of cardiovascular disease. Diabetologia. 2012;55((Leiter L.) University of Toronto, Canada):S310-S1.
Meeting abstract

Leiter LA, Carr MC, Stewart M, et al. Harmony 8: Once weekly (QW) GLP1 Agonist Albiglutide (Albi) vs. Sitagliptin (Sita) in Type 2 Diabetes (T2D) Pts With Renal Impairment (RI): Week 26 Results. Diabetes. 2013;62((Leiter L.A.; Carr M.C.; Stewart M.; Jonesleone A.R.; Yang F.; Handelsman Y.) Toronto, ON, Canada, King of Prussia, PA, Tarzana, CA):A17.
Meeting abstract

Leiter LA, Cefalu WT, de Bruin TW, et al. Dapagliflozin Added to Usual Care in Individuals with Type 2 Diabetes Mellitus with Preexisting Cardiovascular Disease: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with a 28-Week Extension. J Am Geriatr Soc. 2014 Jun 2PMID: 24890683.
Background medications; Placebo-controlled trial

Leiter LA, Cefalu WT, Debruin TW, et al. Efficacy and safety of dapagliflozin for type 2 diabetes mellitus patients with a history of cardiovascular disease [abstract]. Diabetes; 2012. p. A287.
Meeting abstract

Leiter LA, Langslet G, Cefalu WT, et al. Canagliflozin demonstrates durable glycemic improvements over 104 weeks compared with glimepiride in subjects with type 2 diabetes mellitus on metformin.

Canadian Journal of Diabetes. 2013;37((Leiter L.A.; Langslet G.; Cefalu W.T.; Ho Yoon K.; Arias P.; Xie J.; Balis D.; Millington D.; Vercruysse F.; Canovatchel W.; Meininger G.) Toronto, ON CAN; Oslo, Norway; Baton Rouge, LA USA; Seoul, Korea; Rosario, Argentina; Raritan, NJ USA; Beerse, Belgium):S27.
Meeting abstract

Leproust S, Dallongeville J, Valensi P, et al. Treatment maintenance duration of dual therapy with metformin and sitagliptin in type 2 diabetes-real-world data from odyssee study. Value in Health. 2014;17(7):A334-A5.
Meeting abstract

Levesque LE, Brophy JM, Dell'Aniello S, et al. Comparative cardiovascular morbidity and mortality of metformin in older adults with diabetes: A population-based cohort study. Pharmacoepidemiology and Drug Safety. 2010;19((Levesque L.E.; Brophy J.M.; Suissa S.) Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada):S2.
Meeting abstract

Levin PA, Wei W, Buysman E, et al. The INITIATOR study: Real-world treatment patterns and outcomes in patients with type 2 diabetes initiating insulin glargine or liraglutide. Diabetologia. 2014;57(1):S53-S4.
Meeting abstract

Lewin A, DeFronzo R, Patel S, et al. Fixed dose combinations of empagliflozin and linagliptin for 52 weeks in drug-naive subjects with type 2 diabetes. Diabetologia. 2014;57(1):S346-S7.
Meeting abstract

Lewin A, DeFronzo RA, Patel S, et al. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes Care. 2015 Mar;38(3):394-402. PMID: 25633662.
No drug comparison of interest

Lewin AJ, Arvay L, Liu D, et al. Efficacy and tolerability of linagliptin added to a sulfonylurea regimen in patients with inadequately controlled type 2 diabetes mellitus: an 18-week, multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther. 2012 Sep;34(9):1909-19 e15. PMID: 22939034.
No drug comparison of interest

Lewin AJ, Arvay L, Liu D, et al. Safety and efficacy of linagliptin as add-on therapy to a sulphonylurea in inadequately controlled type 2 diabetes. Diabetologia. 2010;53((Lewin A.J.) National Research Institute, Los Angeles, United States):S326.
Meeting abstract

Lewis J, Ferrara A, Peng T, et al. Relative risk of bladder cancer with pioglitazone for diabetes mellitus: Mid-way report of a 10-year follow-up study. Pharmacoepidemiology and Drug Safety. 2010;19((Lewis J.; Bilker W.; Nessel L.; Strom B.) Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, United States):S13.
Meeting abstract

Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care. 2011 Apr;34(4):916-22. PMID: 21447663.
No drug comparison of interest

Lewis JD, Habel L, Quesenberry C, et al. Proteinuria testing among patients with diabetes mellitus is associated with bladder cancer diagnosis: potential for unmeasured

confounding in studies of pioglitazone and bladder cancer. Pharmacoepidemiol Drug Saf. 2014 Jun;23(6):636-45. PMID: 24764283.
No drug comparison of interest; Background medications

Li D, Yeung SC, Hassan MM, et al. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology. 2009 Aug;137(2):482-8. PMID: 19375425.
Background medications

Li H, Cui R, Cai H, et al. The effect of thiazolidinediones on bone mineral density in Chinese older patients with type 2 diabetes. J Bone Miner Metab. 2010;28(1):77-81. PMID: 19603247.
No drug comparison of interest; Does not meet study design criteria

Li P, Chen W, Li L, et al. Glyburide/metformin therapy for patients with type 2 diabets-a multi-center, randomized double-masked study. Chinese Pharmaceutical Journal. 2011;46(17):1362-5.
Non-English language

Li Q, Chitnis A, Hammer M, et al. Real-world clinical and economic outcomes of liraglutide versus sitagliptin in patients with type 2 diabetes mellitus in the United States. Diabetes Ther. 2014 Dec;5(2):579-90. PMID: 25256818.
Does not meet study design criteria; No outcome of interest

Li Y, Hu Y, Rajpathak S, et al. Sulfonylurea use and risk of coronary heart disease among patients with type 2 diabetes: A prospective cohort study among women. Diabetes. 2014;63((Li Y.; Hu Y.; Rajpathak S.; Hu F.B.) Boston, MA, Whiteh - ouse Station, NJ):A372.
Meeting abstract

Liang H, Perez A, Yang J, et al. Event rate assessment of myocardial infarction and stroke for pioglitazone relative to insulin in patients with type 2 diabetes mellitus. Diabetologia. 2012;55((Liang H.; Perez A.; Vallarino C.; Fusco G.; Joseph G.) Takeda Global Research and Development Center, Inc, Deerfield, United States):S498-S9.
Meeting abstract

Lieverse L, Rodriguez M, Czupryniak L, et al. Improved glycaemic control with once-daily insulin glargine in people with type 2 diabetes inadequately controlled on insulin detemir/OAD combination therapy (RESOLUTE). Diabetologia. 2012;55((Lieverse L.) Maxima Medical Centre, Eindhoven, Netherlands):S389.
Meeting abstract

Lin HC, Hsu YT, Kachingwe BH, et al. Dose effect of thiazolidinedione on cancer risk in type 2 diabetes mellitus patients: a six-year population-based cohort study. J Clin Pharm Ther. 2014 Mar 24PMID: 24661226.
No drug comparison of interest

Lin HC, Kachingwe BH, Lin HL, et al. Effects of metformin dose on cancer risk reduction in patients with type 2 diabetes mellitus: a 6-year follow-up study. Pharmacotherapy. 2014 Jan;34(1):36-45. PMID: 23864581.
No drug comparison of interest; Background medications

Lin J, Wei W, Vlajnic A, et al. Real-world practice pattern and outcomes of patients with type 2 diabetes (T2DM) initiating injectable therapy via insulin glargine disposable pen (GLA-P) or liraglutide (LIRA). Diabetes. 2012;61((Lin J.; Wei W.; Vlajnic A.; Pan C.; Xie L.; Baser O.; Levin P.) Flemington, United States):A286.

Meeting abstract

Lind M, Hirsch IB, Tuomilehto J, et al. Design and methods of a randomised double-blind trial of adding liraglutide to control HbA1c in patients with type 2 diabetes with impaired glycaemic control treated with multiple daily insulin injections (MDI-Liraglutide trial). Prim Care Diabetes. 2015 Feb;9(1):15-22. PMID: 25175385.
No drug comparison of interest; Placebo-controlled trial; Background medications

Lind M, Jendle J, Torffvit O, et al. Glucagon-like peptide 1 (GLP-1) analogue combined with insulin reduces HbA1c and weight with low risk of hypoglycemia and high treatment satisfaction. Prim Care Diabetes. 2012 Apr;6(1):41-6. PMID: 22015237.
No drug comparison of interest

Lipscombe LL. Rosiglitazone was non-inferior to metformin plus sulphonylurea for CV events but increased risk of HF and fractures in type 2 diabetes. Evidence-Based Medicine. 2009;14(6):168.
No original data

Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care. 2011 Jun;34(6):1431-7. PMID: 21617112.
No original data

List J, Sonesson C, Gause-Nilsson I, et al. No increased risk of early or late adjudicated cardiovascular events with dapagliflozin. Circulation. 2014;130((List J.; Ptaszynska A.) Metabolic Diseases, Bristol-Myers Squibb, Princeton, United States).
Little MW, Pugh TFG, Carey FJ, et al. The potential protective effect of metformin against pancreatic cancer: A case-control study in two UK centres. Pancreatology. 2011;11(3):311.

Meeting abstract

Liu J, Oh R, Wilson C, et al. Improvement in postprandial glucose after 2-year treatment with alogliptin in patients with type 2 diabetes inadequately controlled with metformin. Diabetologia. 2014;57(1):S365.
Meeting abstract

Liu J, Oh R, Wilson C, et al. Improvement in postprandial glucose after a 2-year treatment with alogliptin in patients with type 2 diabetes inadequately controlled with metformin. Diabetes. 2014;63((Liu J.; Oh R.; Wilson C.; Camisasca R.) Deerfield, IL, London, United Kingdom):A614.
Meeting abstract

Liu J, Raanan M, Spanheimer R, et al. Pioglitazone improves 2-hour glucose level after OGTT in patients with type 2 diabetes. Canadian Journal of Diabetes. 2009;33(3):272-3.
Meeting abstract

Liu YL, Chiang CW, Tsai TR, et al. Comparing the risk for atrial fibrillation in patients with diabetes initiating metformin or sulfonylureas: A nationwide population-based cohort study in Taiwan. Pharmacoepidemiology and Drug Safety. 2014;23((Liu Y.L.; Tsai T.R.) Kaohsiung Medical University, Kaohsiung City, Taiwan):371.
Meeting abstract

Liu Z, Brodovicz KG, Kou D, et al. Influence of time dependent covariates on estimation of risk of acute myocardial infarction comparing sulfonylurea with metformin in type 2 diabetes. Pharmacoepidemiology and Drug Safety. 2012;21((Liu Z.; Brodovicz K.G.; Kou D.; Golm G.T.; Watson D.J.; Girman C.J.) Merck, Whitehouse Station, United States):263.

Meeting abstract

Ljunggren O, Bolinder J, Johansson L, et al. Dapagliflozin has no long-term effect on markers of bone turnover or bone mineral density in patients with inadequately controlled type 2 diabetes on metformin. Diabetologia. 2012;55((Ljunggren O.; Johansson L.) Uppsala University, Stockholm, Sweden):S306-S7.
Meeting abstract

Lockman KA, Teoh WL, Richards MG, et al. Exenatide does not improve liver enzymes despite promoting significant weight loss and HbA1c reduction. Diabetic Medicine. 2010;27(2):160-1.
Meeting abstract

Loebstein R, Dushinat M, Vesterman-Landes J, et al. Database evaluation of the effects of long-term rosiglitazone treatment on cardiovascular outcomes in patients with type 2 diabetes. J Clin Pharmacol. 2011 Feb;51(2):173-80. PMID: 20484611.
Does not account for confounding

Loebstein R, Vasterman-Landes J, Silverman B, et al. Database evaluation of adverse cardiovascular outcomes, related to rosiglitazone (RSG), in the treatment of type 2 diabetes mellitus (T2DM) patients in the community. Clinical Pharmacology and Therapeutics. 2009;85((Loebstein R.; Vasterman-Landes J.; Silverman B.; Dushinat M.; Friedman N.; Lomnick Y.; Kokia E.; Halkin H.) Maccabi Healthcare Services, Tel Aviv, Israel):S7.
Meeting abstract

Lopez JM, Martin S, Ektare V, et al. Short-term economic and clinical outcomes of canagliflozin compared to sitagliptin in the management of type 2 diabetes mellitus (T2DM). Value in Health. 2014;17(3):A251.
Meeting abstract

Lu CJ, Sun Y, Muo CH, et al. Risk of stroke with thiazolidinediones: a ten-year nationwide population-based cohort study. Cerebrovasc Dis. 2013;36(2):145-51. PMID: 24029780.
Does not meet study design criteria

Lu DY, Leu HB. Metformin and risk of deep vein thrombosis: A nonrandomized, pair-matched cohort study. Journal of the American College of Cardiology. 2014;63(12):A2099.
Meeting abstract

Lu Y, Mei-Qing S, Qiu-Ling Z, et al. Effect of Piglitazone and Metformin on Retinol-binding Protein-4 and Adiponcetin in Patients with Type 2 Diabetes Mellitus Complicated with Non-alcohol Fatty Acid Liver Diseases. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2014 Jun 28;36(3):309-12. PMID: 24997826.
Non-English language

Lu ZH, Pan CY, Gao Y, et al. [A randomized, double blind, placebo-controlled, parallel and multicenter study to evaluate the safety and efficacy of pioglitazone with sulphonylurea in type 2 diabetic patients]. Zhonghua Nei Ke Za Zhi. 2011 Oct;50(10):826-30. PMID: 22321321.
No drug comparison of interest

Lundby-Christensen L, Almdal T, Tarnow L, et al. Effect of three insulin analogue regimens on carotid intima-media thickness in patients with type 2 diabetes-the randomized copenhagen insulin and metformin therapy (CIMT) trial. Diabetes. 2014;63((Lundby-Christensen L.; Almdal T.; Tarnow L.; Wiinberg N.; Vestergaard H.; Thorsteinsson B.; Snorgaard O.; Gade-Rasmussen B.; Breum L.; Mathiesen E.R.; Jensen T.; Hemmingsen B.; Boesgaard T.W.; Lund S.S.; Perrild H.; Hedetoft C.;

Roder M.; Krarup T.; Sneppen S.B.; Duun E.; Peder Sen O.B.; Carstensen B.; Gluud C.; Wetterslev J.; Vaag A.A.; Madsbad S.) Hvidovre, Denmark, Gentofte, Denmark, Hillerod, Denmark, Frederiks berg, Denmark, Copenhagen, Denmark, Koge, Denmark, Ingelheim, Germany):A116.
Meeting abstract

Luo J, Beresford S, Chen C, et al. Association between diabetes, diabetes treatment and risk of developing endometrial cancer. Br J Cancer. 2014 Sep 23;111(7):1432-9. PMID: 25051408.
Does not account for confounding; Background medications

Ma L, Wu N, Russo PA, et al. Comparative study of rosiglitazone versus sulfonylurea as add-on therapy: Economic analysis of type 2 diabetes mellitus. American Journal of Pharmacy Benefits. 2012;4(1):e1-e7.
No outcome of interest

Macconell L, Brown C, Gurney K, et al. Safety and tolerability of exenatide twice daily in patients with type 2 diabetes: integrated analysis of 5594 patients from 19 placebo-controlled and comparator-controlled clinical trials. Diabetes Metab Syndr Obes. 2012;5:29-41. PMID: 22375098.
Background medications; No drug comparison of interest

MacConell L, Chen S, Gurney K, et al. Safety and tolerability of GLP-1 receptor agonists in patients with type 2 diabetes in comparator-controlled DURATION trials. Diabetologia. 2012;55((MacConell L.; Chen S.; Gurney K.; Malloy J.; Zhang H.; Zhou M.; Kolterman O.) Amylin Pharmaceuticals, Inc., San Diego, United States):S329.
Meeting abstract

Macconell L, Gurney K, Malloy J, et al. Safety and tolerability of exenatide once weekly in patients with type 2 diabetes: An integrated analysis of 4328 patients. Diabetes. 2012;61((Macconell L.; Gurney K.; Malloy J.; Zhang H.; Zhou M.; Chen S.) San Diego, United States):A598.
Meeting abstract

MacDonald MR, Eurich DT, Majumdar SR, et al. Treatment of type 2 diabetes and outcomes in patients with heart failure: a nested case-control study from the U.K. General Practice Research Database. Diabetes Care. 2010 Jun;33(6):1213-8. PMID: 20299488.
Does not meet study design criteria; Background medications

MacDonald MR, Petrie MC, Home PD, et al. Incidence and prevalence of unrecognized myocardial infarction in people with diabetes: a substudy of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study. Diabetes Care. 2011 Jun;34(6):1394-6. PMID: 21562320.
Background medications; No drug comparison of interest

Machado HA, Vieira M, Cunha MR, et al. Metformin, but not glimepiride, improves carotid artery diameter and blood flow in patients with type 2 diabetes mellitus. Clinics (Sao Paulo). 2012 Jul;67(7):711-7. PMID: 22892913.
Does not meet study design criteria; No drug comparison of interest

Maeda H, Kubota A, Kanamori A, et al. Long-term efficacy and safety of sitagliptin in the treatment of Japanese Type 2 diabetes (ASSET-K1) to a target of HbA1c <7%. J Endocrinol Invest. 2013 Sep;36(8):568-73. PMID: 23385888.

No drug comparison of interest; Background medications

Mafauzy M, Hussein Z, Chan SP. The Status of Diabetes Control in Malaysia: Results of Diabcare 2008. Medical Journal of Malaysia. 2011;66(3):175-81.
No drug comparison of interest

Maffioli P, D'Angelo A, Perrone T, et al. Ultrasonography modifications of visceral and subcutaneous adipose tissue after pioglitazone or glibenclamide therapy combined with rosuvastatin in type 2 diabetic patients not well controlled by metformin. Diabetes. 2013;62((Maffioli P.; D'Angelo A.; Perrone T.; Fogari E.; Derosa G.) Pavia, Italy):A288.
Meeting abstract

Maffioli P, Franzetti IG, Querci F, et al. Exenatide plus metformin compared to metformin alone on beta cell function in type 2 diabetic patients. Diabetologia. 2012;55((Maffioli P.; Fogari E.; Derosa G.) Internal Medicine and Therapeutics, University of Pavia, IRCCS Policlinico S.Matteo, Pavia, Italy):S298.
Meeting abstract

Magliano DJ, Davis WA, Shaw JE, et al. Incidence and predictors of all-cause and site-specific cancer in type 2 diabetes: The Fremantle Diabetes Study. European Journal of Endocrinology. 2012;167(4):589-99.
Background medications

Maguire A, Mitchell B. Effectiveness of oral antidiabetic drugs in treatment naive patients: Trends in HbA1c in the UK. Diabetologia. 2012;55((Maguire A.) Epidemiology and Database Analytics, UBC, London, United Kingdom):S26.
Meeting abstract

Mahaffey KW, Hafley G, Dickerson S, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J. 2013 Aug;166(2):240-9 e1. PMID: 23895806.
No drug comparison of interest; Background medications

Maheux P, Allen E, Ravichandran S, et al. Saxagliptin added to a thiazolidinedione, metformin or a sulphonylurea improves glycaemic control in patients with inadequately controlled type 2 diabetes mellitus. Endocrine Abstracts. 2010;20((Maheux P.) AstraZeneca ISMO Europe, Brussels, Belgium):P338.
Meeting abstract

Maheux P, Doucet J, Allen E, et al. Efficacy and safety of saxagliptin 5 mg once-daily therapy in elderly patients with type 2 diabetes mellitus. Diabetologia. 2009;52(S1):S302.
Meeting abstract

Mahmood IH, Nazar W. Effects of glibenclamide and metformin on prevalence of metabolic syndrome in type 2 diabetic patients. Pakistan Journal of Medical Sciences. 2011;27(5):1033-7.
Does not meet study design criteria

Makdissi A, Ghanim H, Vora M, et al. Sitagliptin exerts an antinflammatory action. J Clin Endocrinol Metab. 2012 Sep;97(9):3333-41. PMID: 22745245.
No drug comparison of interest

Malloy J, Meloni A, Han J. Efficacy and tolerability of exenatide once weekly versus sitagliptin in patients with type 2 diabetes mellitus: a retrospective analysis of pooled clinical trial data. Postgrad Med. 2013 May;125(3):58-67. PMID: 23748507.
No drug comparison of interest

Malone J, Walsh B, Pencek R, et al. Efficacy and safety of exenatide once weekly across background therapies: A pooled analysis of DURATION studies. Diabetologia. 2011;54((Malone J.; Bruhn D.) Eli Lilly and Company, Indianapolis, United States):S314.
Meeting abstract

Mamtani R, Haynes K, Bilker WB, et al. Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. J Natl Cancer Inst. 2012 Sep 19;104(18):1411-21. PMID: 22878886.
Does not account for confounding

Mamtani R, Haynes K, Bilker WB, et al. Long-term therapy with thiazolidinediones and the risk of bladder cancer: A cohort study. Journal of Clinical Oncology. 2012;30(15).
Meeting abstract

Mamtani R, Haynes K, Bilker WB, et al. Long-term therapy with thiazolidinediones may be associated with increased incidence of bladder cancer. Pharmacoepidemiology and Drug Safety. 2012;21((Mamtani R.; Vaughn D.J.) Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, United States):25.
Meeting abstract

Mamtani R, Pfanzelter N, Haynes K, et al. Incidence of bladder cancer in patients with type 2 diabetes treated with metformin or sulfonylureas. Diabetes Care. 2014 Jul;37(7):1910-7. PMID: 24496803.
Does not meet study design criteria

Mancini T, Mazziotti G, Doga M, et al. Vertebral fractures in males with type 2 diabetes treated with rosiglitazone. Bone. 2009 Oct;45(4):784-8. PMID: 19527806.
Does not meet study design criteria

Mannucci E, Zinman B, Moses A, et al. Cardiovascular safety of liglutide: A pooled analysis from phase 2 and 3 liraglutide clinical development studies. High Blood Pressure and Cardiovascular Prevention. 2012;19(2):108-9.
Meeting abstract

Mansfield TA, De Bruin T, Hardy E, et al. Glycaemic and weight-reduction benefits with dapagliflozin in patients with type 2 diabetes mellitus: Pooled subgroup analysis of nine clinical trials. Diabetologia. 2012;55((Mansfield T.A.) Bristol-Myers Squibb, Princeton, United States):S310.
Meeting abstract

Marso S, Jensen T, Moses A, et al. Cardiovascular safety of liraglutide: A pooled analysis from phase 2 and 3 liraglutide clinical development studies. Journal of Diabetes. 2011;3((Marso S.) Saint Luke's Mid America Heart Institute, Kansas City, United States):15.
Meeting abstract

Marso SP, Lindsey JB, Stolker JM, et al. Cardiovascular safety of liraglutide assessed in a patient-level pooled analysis of phase 2-3 liraglutide clinical development studies. Diabetes and Vascular Disease Research. 2011;8(3):237-40.
Background medications

Martin CK, Gupta AK, Smith SR, et al. Effect of pioglitazone on energy intake and ghrelin in diabetic patients. Diabetes Care. 2010 Apr;33(4):742-4. PMID: 20067964.
Martin S, Henk H, Chow W. Clinical and demographic characteristics of people with type 2 diabetes mellitus (T2DM) initiating canagliflozin from a united states managed care sample. Value in Health. 2014;17(3):A261.

No outcome of interest

Martinez L, Gourdy P, Eschwege E, et al. Baseline observations from the EVIDENCE Study: Characteristics of type 2 diabetes patients initiating liraglutide. Primary Care Diabetes. 2013;7(1):77.
Meeting abstract

Martin-Merino E, Fortuny J, Rivero E, et al. Risk factors for incident diabetic macular edema in type II diabetes in UK primary care. Pharmacoepidemiology and Drug Safety. 2012;21((Martin-Merino E.; Garcia-Rodriguez L.A.) Centro Espanol de Investigacion Farmacoepidemiologica CEIFE, Madrid, Spain):272-3.
Meeting abstract

Marx N, Rosenstock J, Kahn S, et al. Baseline characteristics of participants enrolled in the cardiovascular outcome study of linagliptin versus glimepiride in early type 2 diabetes (Carolina). Diabetes. 2013;62((Marx N.; Rosenstock J.; Kahn S.; Zinman B.; Kastelein J.J.; Lachin J.M.; Bluhmki E.; Mattheus M.; Patel S.; Erik Johansen O.; Woerle H.-J.) Aachen, Germany, Dallas, TX, Seattle, WA, Toronto, ON, Canada, Amsterdam, Netherlands, Rockville, MD, Ingelheim, Germany, Bracknell, United Kingdom):A602.
Meeting abstract

Masica A, Daoud Y, West S. Impact of oral antidiabetic drugs on development of chronic kidney disease. Pharmacoepidemiology and Drug Safety. 2011;20((Masica A.; Daoud Y.) Baylor Health Care System, Dallas, United States):S327.
Meeting abstract

Matsuhashi T, Sano M, Fukuda K, et al. Sitagliptin counteracts seasonal fluctuation of glycemic control. World J Diabetes. 2012 Jun 15;3(6):118-22. PMID: 22737282.
Background medications; Does not meet study design criteria

Matsumoto Y. Retrospective survey evaluating exenatide twice daily in obese patients with type 2 diabetes mellitus. Therapeutic Research. 2014;35(12):1107-16.
Non-English language

Matsushita T, Kaji A, Kaji K, et al. Effects of pioglitazone and metformin combination therapy on high-molecular-weight adiponectin compared with metformin monotherapy in type 2 diabetes mellitus patients. Diabetes. 2012;61((Matsushita T.; Kaji A.; Kaji K.; Takahashi E.; Usui T.; Asahi N.; Sato T.; Ohono A.; Ueki A.) Tokyo, Japan):A626.
Meeting abstract

Matthaei S. [Canagliflozin monotherapy: clinical study data in type 2 diabetes mellitus]. Dtsch Med Wochenschr. 2014 Feb;139 Suppl 2:S59-64. PMID: 24481634.
Placebo-controlled trial; No original data

Matthews D, Colagiuri S, Frid A, et al. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, reduces systolic blood pressure in subjects with Type 2 diabetes. Diabetic Medicine. 2009;26((Matthews D.) Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, United Kingdom):128-9.
Meeting abstract

Matthews D, Jendle J, Nauck M, et al. Liraglutide, a once-daily human GLP-1 analogue, reduces fat percentage and visceral and subcutaneous adipose tissue compared with glimepiride when added to metformin in subjects with Type 2 diabetes. Diabetic Medicine. 2009;26((Matthews D.)

Oxford Centre for Diabetes Endocrinology and Metabolism, University of Oxford, Oxford, United Kingdom):21-2.
Meeting abstract

Matthews D, Zinman B, Tong C, et al. Glycemic efficacy of canagliflozin (CANA) is largely independent of baseline beta-cell function or insulin sensitivity. Diabetes. 2014;63((Matthews D.; Zinman B.; Tong C.; Meininger G.; Polidori D.) Oxford, United Kingdom, Toronto, ON, Canada, Raritan, NJ, San Diego, CA):A285.
Meeting abstract

Matthews JE, Ahren B, Ye J, et al. Harmony 3 year 3 Results: Albiglutide vs sitagliptin and glimepiride in patients with type 2 diabetes mellitus on metformin. Diabetologia. 2014;57(1):S337.
Meeting abstract

Mawatari K, Tahara N, Yasukawa H, et al. Pioglitazone decreases plasma fibroblast growth factor-21 levels in patients with type 2 diabetes. Circulation. 2012;126(21).
Meeting abstract

McAdam-Marx C, Bellows BK, Wygant GD, et al. Association of (greater-than or equal to)5% weight loss and self-reported adherence with 6-month glycemic control in type 2 diabetes mellitus (T2DM): The DELTA study. Diabetes. 2013;62((Mcadam-Marx C.; Bellows B.K.; Wygant G.D.; Mukherjee J.; Unni S.; Ye X.; Liberman J.; Iloeje U.H.; Brixner D.) Salt Lake City, UT, Princeton, NJ, Wallingford, CT, Sacramento, CA):A321.
Meeting abstract

McAdam-Marx C, Brixner D, Ye X, et al. A1C and weight outcomes following 6 months of analog basal insulin in insulin naive patients with type-2 diabetes in an ambulatory care setting. Value in Health. 2009;12(3):A97.
Meeting abstract

McAdam-Marx C, Mukherjee J, Bellows BK, et al. Evaluation of the relationship between weight change and glycemic control after initiation of antidiabetic therapy in patients with type 2 diabetes using electronic medical record data. Diabetes Res Clin Pract. 2014 Mar;103(3):402-11. PMID: 24503045.
Does not meet study design criteria

McAdam-Marx C, Yu J, Shankar V, et al. Average daily dose of analog basal insulins in patients with type 2 diabetes: A matched case control analysis. Canadian Journal of Diabetes. 2009;33(3):295-6.
Meeting abstract

McCall TB, Bron M, Liu J, et al. High-density lipoprotein cholesterol-improving advantage of pioglitazone compared with non-TZD oral medications. Diabetes. 2009;58((Mccall T.B.; Bron M.; Liu J.; Manthena S.; Spanheimer R.) Deerfield, United States).
Meeting abstract

McCormic LM, Kyd AC, Rea PA, et al. Chronic DPP-4 inhibition by sitagliptin enhances both global and regional myocardial function during dobutamine stress in patients with type 2 diabetes mellitus and coronary artery disease. Heart. 2012;98((McCormic L.M.; Kyd A.C.; Rea P.A.; Hool S.P.; Dutk D.P.) Department of Cardiovascular Medicine, University of Cambridge, Cambridge, United Kingdom):A73.
Meeting abstract

McCormick LM, Kydd AC, Read PA, et al. Chronic dipeptidyl peptidase-4 inhibition with sitagliptin is associated with sustained

protection against ischemic left ventricular dysfunction in a pilot study of patients with type 2 diabetes mellitus and coronary artery disease. Circ Cardiovasc Imaging. 2014 Mar;7(2):274-81. PMID: 24503784.
No outcome of interest; Follow-up less than 3 months

McEwan P, Evans ML, Nyeland ME, et al. Impact of UK guidelines on clinical prescribing in patients with Type 2 diabetes: A comparative effectiveness analysis of liraglutide vs sitagliptin in the UK. Diabetic Medicine. 2014;31((McEwan P.) Swansea Centre for Health Economics, Swansea University, Cardiff, United Kingdom):174.
Meeting abstract

McGavock J, Szczepaniak LS, Ayers CR, et al. The effects of rosiglitazone on myocardial triglyceride content in patients with type 2 diabetes: a randomised, placebo-controlled trial. Diab Vasc Dis Res. 2012 Apr;9(2):131-7. PMID: 22067724.
Background medications; Pleacebo-controlled trial

McGill JB, Sloan L, Newman J, et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: A 1-year, randomized, double-blind, placebo-controlled study. Diabetes Care; 2013. p. 237-44.
Background medications

McGill JB, Sloan L, Newman J, et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: a 1-year, randomized, double-blind, placebo-controlled study. Diabetes Care. 2013 Feb;36(2):237-44. PMID: 23033241.
Background medications; Comorbidity

McGuire DK, Abdullah SM, See R, et al. Randomized comparison of the effects of rosiglitazone vs. placebo on peak integrated cardiovascular performance, cardiac structure, and function. Eur Heart J. 2010 Sep;31(18):2262-70. PMID: 20601395.
Background medications

Medin J, Grandy S, Rohwedder K, et al. Effects of dapagliflozin on patient reported treatment satisfaction in patients with type 2 diabetes mellitus: Results from two double-blind trials. Diabetologia. 2011;54((Medin J.) HEOR, AstraZeneca, Molndal, Sweden):S346.
Meeting abstract

Megarbane B, Adjibade AN, Touizer E, et al. Metformin-associated lactic acidosis (MALTA) in the intensive care unit: Outcome and toxicokinetic analysis. Clinical Toxicology. 2009;47(5):496.
Meeting abstract

Meichun Ko E, Franasiak J, Clark LH, et al. Impact of metformin use on risk of recurrence in high-grade endometrial cancers. Journal of Clinical Oncology. 2012;30(15).
Meeting abstract

Meier JJ, Nauck MA. Risk of pancreatitis in patients treated with incretin-based therapies. Diabetologia. 2014 Jul;57(7):1320-4. PMID: 24723174.
Does not account for confounding

Meininger G, Wysham C, Woo V, et al. Canagliflozin added on to dipeptidyl peptidase-4 inhibitors or glucagon-like peptide-1 agonists with or without other antihyperglycaemic agents in type 2 diabetes mellitus. Diabetologia. 2013;56((Meininger G.; Capuano G.; Alba M.; Desai M.) Janssen Research and Development, LLC, Raritan, United States):S373.
Meeting abstract

Meloni AR, DeYoung MB, Han J, et al. Treatment of patients with type 2 diabetes with exenatide once weekly versus oral glucose-lowering medications or insulin glargine: achievement of glycemic and cardiovascular goals. Cardiovasc Diabetol. 2013;12:48. PMID: 23522121.
Handsearch

Meneghini LF, Rosenberg N, Hollander P, et al. Effects of insulin glargine vs thiazolidinediones on glycemic and lipid variables in type 2 diabetes mellitus (T2DM): The impact of obesity. Diabetes. 2009;58((Meneghini L.F.; Rosenberg N.; Hollander P.; Rosenstock J.; Riddle M.C.; Nesto R.W.; Dandona P.)).
Meeting abstract

Meneghini LF, Traylor L, Schwartz SL. Improved glycemic control with insulin glargine versus pioglitazone as add-on therapy to sulfonylurea or metformin in patients with uncontrolled type 2 diabetes mellitus. Endocr Pract. 2010 Jul-Aug;16(4):588-99. PMID: 20350924.
Background medications; No drug comparison of interest

Mensberg P, Nyby S, Jorgensen PG, et al. Near-normalization of glycemic control in patients with type 2 diabetes with a glucagon-like peptide-1 receptor agonist in combina tion with exercise training: A randomized, double-blinded, placebo-controlled clinical trial. Diabetes. 2014;63((Mensberg P.; Nyby S.; Jorgensen P.G.; Storgaard H.; Sivertsen J.; Jensen M.T.; Holst J.J.; Kiens B.; Richter E.A.; Knop F.K.; Vilsboll T.) Hellerup, Denmark, Copenhagen, Denmark):A182.
Meeting abstract

Merker L, Haring HU, Christiansen AV, et al. Empagliflozin (EMPA) for (greater-than or equal to)76 weeks as add-on to metformin in patients with type 2 diabetes (T2DM). Diabetes. 2014;63((Merker L.; Haring H.-U.; Christiansen A.V.; Roux F.; Salsali A.; Kim G.; Meinicke T.; Woerle H.J.; Broedl U.C.) Dormagen, Germany, Tubingen, Germany, Copenhagen, Denmark, Reims, France, Ingelheim, Germany):A278.
Meeting abstract

Merker L, Lund SS, Hantel S, et al. Efficacy and safety of empagliflozin (EMPA) in younger, overweight/ obese patients with type 2 diabetes (T2DM) with HbA1c (greater-than or equal to)8%. Diabetes. 2014;63((Merker L.; Lund S.S.; Hantel S.; Salsali A.; Kim G.; Broedl U.C.; Woerle H.J.; Hach T.) Dormagen, Germany, Ingelheim, Germany, Biberach, Germany):A280-A1.
Meeting abstract

Mijares AH. DPP-4 inhibitors vs GLP-1 receptor agonists after failure of metformin monotherapy in type 2 diabetes. Avances en Diabetologia. 2010;26(3):200-2.
No original data

Miller CG, Nino AJ, Bilezikian JP, et al. Evaluation of QCT cortical hip parameters in a clinical trial with rosiglitazone: Potential for a new study endpoint. Osteoporosis International. 2012;23((Miller C.G.) Bioclinica, Inc., Medical Affairs, Yardley, United States):S275-S6.
Meeting abstract

Miller LA, Burudpakdee C, Zagar A, et al. Exenatide (BID) and liraglutide (QD) treatment patterns among type-2 diabetes patients in Germany. Value in Health. 2011;14(3):A103-A4.
Meeting abstract

Miller LA, Burudpakdee C, Zagar A, et al. Exenatide BID and liraglutide QD treatment patterns among type 2 diabetes patients in

Germany. J Med Econ. 2012;15(4):746-57. PMID: 22443463.
Background medications

Minervini G, Cook W, Bryzinski B, et al. Efficacy and safety of saxagliptin in patients with type 2 diabetes mellitus and cardiovascular disease history or cardiovascular risk factors. Endocrine Practice. 2014;20(1):35A.
Meeting abstract

Mirmiranpour H, Mousavizadeh M, Noshad S, et al. Comparative effects of pioglitazone and metformin on oxidative stress markers in newly diagnosed type 2 diabetes patients: a randomized clinical trial. J Diabetes Complications. 2013 Sep-Oct;27(5):501-7. PMID: 23891275.
No drug comparison of interest; No outcome of interest

Mishra M, Kumar H, Pokharia D, et al. Effect of pioglitazone, rosiglitazone and glipizide on NOx, TNF-(alpha), VEGF, angiogenin in type 2 diabetes mellitus with cardiovascular complications. Diabetes. 2009;58((Mishra M.; Kumar H.; Pokharia D.; Arya A.K.; Bajpai S.; Singh R.K.; Rai M.; Tripathi K.) Varanasi, India).
Meeting abstract

Mitchell BD, Eby EL, Lage MJ. Glycemic control and the first use of oral antidiabetic agents among patients with type 2 diabetes mellitus. Curr Med Res Opin. 2013 Dec;29(12):1587-97. PMID: 23886028.
Does not apply; Does not meet study design criteria

Mithal A, Barnett AH, Manassie J, et al. Empagliflozin in patients with type 2 diabetes mellitus and stage 3A, 3B and 4 chronic kidney disease (CKD). Diabetologia. 2013;56((Mithal A.) Medanta - the Medicity, Gurgaon, Delhi NCR, India):S382.
Meeting abstract

Mitry M, Forst T, Michelson G, et al. Addition of liraglutide improves retinal endothelial function and vascular risk profile in type 2 diabetic patients well controlled by metformin monotherapy. Diabetologia. 2011;54((Mitry M.; Forst T.) Medical, Institute for Clinical Research and Development, Mainz, Germany):S454-S5.
Meeting abstract

Mitry M, Forst T, Michelson G, et al. Pilot study on the effect of liraglutide on retinal microvascular function in type 2 diabetic patients. Diabetes. 2011;60((Mitry M.; Forst T.; Michelson G.; Ratter F.; Wilhelm B.; Pfutzner A.) Mainz, Germany):A264-A5.
Meeting abstract

Mitsutake R, Urata H, Okamura K, et al. Effect of alogliptin on blood pressure in patients with type 2 diabetes mellitus. Journal of the American Society of Hypertension. 2014;8(4):e109.
Meeting abstract

Mizoguchi M, Tahara N, Tahara A, et al. Pioglitazone attenuates atherosclerotic plaque inflammation in patients with impaired glucose tolerance or diabetes a prospective, randomized, comparator-controlled study using serial FDG PET/CT imaging study of carotid artery and ascending aorta. JACC Cardiovasc Imaging. 2011 Oct;4(10):1110-8. PMID: 21999871.
No type 2 diabetes; Background medications

Mogensen UM, Andersson C, Fosbol EL, et al. DPP-4 inhibitors and GLP-1 agonists in type 2 diabetes - Early assessment of cardiovascular safety in a nationwide setting. European Heart Journal.

2013;34((Mogensen U.M.; Fosbol E.L.; Kober L.) Rigshospitalet - Copenhagen University Hospital, Heart Centre, Department of Cardiology, Copenhagen, Denmark):1111.
Meeting abstract

Monami M, Colombi C, Balzi D, et al. Metformin and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care. 2011 Jan;34(1):129-31. PMID: 20980415.
No drug comparison of interest; Background medications

Monami M, Dicembrini I, Kundisova L, et al. A meta-analysis of the hypoglycaemic risk in randomized controlled trials with sulphonylureas in patients with type 2 diabetes. Diabetes Obes Metab. 2014 Mar 17PMID: 24635837.
Handsearch

Montanya E, Colagiuri S, Blonde L, et al. A1C improvement with liraglutide evaluated by baseline BMI. Canadian Journal of Diabetes. 2013;37((Montanya E.; Colagiuri S.; Blonde L.; Bo Svendsen C.; Farah L.; Nauck M.) Barcelona, Spain; Sydney, Australia; New Orleans, LA USA; Soborg, Denmark; Mississauga, ON CAN; Bad Lauterberg, Germany):S35-S6.
Meeting abstract

Montanya E, Pratley R, Nauck M, et al. Switching from sitagliptin to liraglutide, in combination with metformin, improves treatment satisfaction in patients with type 2 diabetes. Diabetes. 2011;60((Montanya E.; Pratley R.; Nauck M.; Bailey T.; Garber A.; Filetti S.; Thomsen A.B.; Hammer M.; Davies M.) Barcelona, Spain):A307.
Meeting abstract

Montilla S, Marchesini G, Sammarco A, et al. Drug utilization, safety, and effectiveness of exenatide, sitagliptin, and vildagliptin for type 2 diabetes in the real world: data from the Italian AIFA Anti-diabetics Monitoring Registry. Nutr Metab Cardiovasc Dis. 2014 Dec;24(12):1346-53. PMID: 25300980.
Background medications

Morgan CL, Jenkins-Jones S, Evans M, et al. Weight change in people with type 2 diabetes: secular trends and the impact of alternative antihyperglycaemic drugs. Diabetes Obes Metab. 2012 May;14(5):424-32. PMID: 22192841.
Does not report long-term outcomes or adverse events

Morgan CL, Mukherjee J, Jenkins-Jones S, et al. Association between first-line monotherapy with sulphonylurea versus metformin and risk of all-cause mortality and cardiovascular events: a retrospective, observational study. Diabetes Obes Metab. 2014 Apr 11PMID: 24720708.
Does snot account for confounding; Background medications

Morgan CL, Mukherjee J, Jenkins-Jones S, et al. Combination therapy with metformin plus sulphonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality. Diabetes Obes Metab. 2014 Apr 25PMID: 24762119.
Does not account for confounding

Morgan CL, Poole CD, Jenkins-Jones S, et al. Weight change for patients with type 2 diabetes: Secular trends and impact of different combinations of therapy. Value in Health. 2010;13(7):A286.
Meeting abstract

Mori H, Okada Y, Arao T, et al. Sitagliptin improves albuminuria in patients with type 2 diabetes mellitus. J Diabetes Investig. 2014 May 4;5(3):313-9. PMID: 24843780.

No drug comparison of interest; Background medications

Mori H, Okada Y, Tanaka Y. Sitagliptin reduces microalbuminuria in patients with type 2 diabetes mellitus. Journal of Diabetes Science and Technology. 2012;6(2):A114-A5.
Meeting abstract

Morikawa A, Ishizeki K, Iwashima Y, et al. Pioglitazone reduces urinary albumin excretion in renin-angiotensin system inhibitor-treated type 2 diabetic patients with hypertension and microalbuminuria: the APRIME study. Clin Exp Nephrol. 2011 Dec;15(6):848-53. PMID: 21823043.
Background medications; No drug comparison of interest

Morling J, Strachan MWJ, Williamson RM, et al. Thiozolidinedione use in people with Type 2 diabetes is associated with regression of hepatosteatosis: The Edinburgh Type 2 Diabetes Study. Diabetic Medicine. 2012;29((Morling J.; Robertson C.M.; Price J.F.) Centre for Population Health Sciences, University of Edinburgh, Edinburgh, United Kingdom):146-7.
Meeting abstract

Mosenzon O, Bhatt DL, Litwak L, et al. Effect of saxagliptin on renal outcomes. Diabetes. 2014;63((Mosenzon O.; Bhatt D.L.; Litwak L.; Shestakova M.; Leibowitz G.; Hirshberg B.; Parker A.; Iqbal N.; Scirica B.M.; Ma R.C.; Raz I.) Jerusalem, Israel, Boston, MA, Buenos Aires, Argentina, Moscow, Russian Federation, Wilmington, DE, Princeton, NJ, Hong Kong, Hong Kong):A140.
Meeting abstract

Mosenzon O, Davidson J, Scirica BM, et al. Incidence of fractures in patients with type 2 diabetes in the SAVOR-TIMI 53 trial. Diabetes. 2014;63((Mosenzon O.; Davidson J.; Scirica B.M.; Leibowitz G.; Bretzel R.G.; Villena J.E.; Hirshberg B.; Stahre C.; Parker A.; Strojek K.; Bhatt D.L.; Raz I.) Jerusalem, Israel, Dallas, TX, Boston, MA, Giessen, Germany, Lima, Peru, Wilmington, DE, Molndal, Sweden, Zabrze, Poland):A265.
Meeting abstract

Motoshima H, Igata M, Takaki Y, et al. Anti-hypertensive effect of sitagliptin in japanese subjects with type 2 diabetes (T2DM) and hypertension (HT)-a continuous Blood Pressure (BP)-lowing effect during one year. Diabetes. 2012;61((Motoshima H.; Igata M.; Takaki Y.; Matsumura T.; Kondo T.; Senokuchi T.; Shimoda S.; Nishikawa T.; Araki E.) Kumamoto, Japan):A273.
Meeting abstract

Mudaliar S, Henry RR, Boden G, et al. Changes in insulin sensitivity and insulin secretion with the sodium glucose cotransporter 2 inhibitor dapagliflozin. Diabetes Technol Ther. 2014 Mar;16(3):137-44. PMID: 24237386.
Background medications; Placebo-controlled trial

Mullugeta Y, Chawla R, Kebede T, et al. Dyslipidemia associated with poor glycemic control in type 2 diabetes mellitus and the protective effect of metformin supplementation. Indian J Clin Biochem. 2012 Oct;27(4):363-9. PMID: 24082461.
No drug comparison of interest; Does not meet study design criteria

Murakami I. Effects of bidirectional switching in sitagliptin, vildagliptin and alogliptin on glucose control in type 2 diabetes mellitus. Therapeutic Research. 2014;35(3):305-11.
Does not meet study design criteria

Murakami T, Kokado H. Antidiabetic monotherapy by linagliptin provides multiple antiatherosclerotic effects independent of diabetic improvement for type-2 diabetics with coronary artery disease. Circulation. 2013;128(22).
Meeting abstract

Murakami T, Mizuno S. Long-term treatment with sitagliptin provides multiple ultrasonic manifested antiatherosclerotic effects independent of diabetic improvement for type-2 diabetics. Circulation. 2013;128(22).
Meeting abstract

Naderi N, May HT, Horne BD, et al. Association of rosiglitazone and pioglitazone to death and myocardial infarction among diabetic patients with coronary artery disease. Journal of the American College of Cardiology. 2009;53(10):A377.
Meeting abstract

Nagai Y, Kato H, Sada Y, et al. Effects of sitagliptin on body fat and intrahepatic lipid content in Japanese overweight patients with type 2 diabetes. Diabetologia. 2014;57(1):S356.
Meeting abstract

Naka KK, Papathanassiou K, Bechlioulis A, et al. Effects of pioglitazone and metformin on vascular endothelial function in patients with type 2 diabetes treated with sulfonylureas. Diab Vasc Dis Res. 2012 Jan;9(1):52-8. PMID: 22049096.
No drug comparison of interest

Naka KK, Papathanassiou K, Bechlioulis A, et al. Effects of pioglitazone versus metformin on endothelial function in patients with type 2 diabetes treated with sulfonylureas. European Heart Journal. 2011;32((Naka K.K.; Pappas K.; Michalis L.K.) Department of Cardiology, University of Ioannina, Ioannina, Greece):65-6.
Meeting abstract

Naka KK, Pappas K, Papathanassiou K, et al. Lack of effects of pioglitazone on cardiac function in patients with type 2 diabetes and evidence of left ventricular diastolic dysfunction: a tissue doppler imaging study. Cardiovasc Diabetol. 2010;9:57. PMID: 20863381.
No drug comparison of interest; Background medications

Nakano K, Hasegawa G, Fukui M, et al. Effect of pioglitazone on various parameters of insulin resistance including lipoprotein subclass according to particle size by a gel-permeation high-performance liquid chromatography in newly diagnosed patients with type 2 diabetes. Endocr J. 2010;57(5):423-30. PMID: 20160397.
Bakground medications

Nandy D, Johnson C, Basu R, et al. The effect of liraglutide on endothelial function in patients with type 2 diabetes. Diab Vasc Dis Res. 2014 Nov;11(6):419-30. PMID: 25212693.
No outcome of interest

Naravadi VVR, Balasubramanian G, Pandit A, et al. Impact of anti-diabetic medications on the prevalence of colorectal neoplasm in patients with type2 diabetes mellitus. American Journal of Gastroenterology. 2012;107((Naravadi V.V.R.; Balasubramanian G.; Pandit A.; Bavani N.; Dhroove G.; Molnar J.) Rosalind Franklin University of Medicine and Science, North Chicago, United States):S234.
Meeting abstract

Narayanan RP, Anderson SG, Onyekwelu E, et al. Vitamin B12 is lower in metformin

treated patients but haemoglobin is unaffected. Diabetic Medicine. 2012;29((Narayanan R.P.; Heald A.H.) Vascular Research Group, University of Manchester, Manchester, United Kingdom):72.
Meeting abstract

Nauck M, del Prato S, Meier JJ, et al. [Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin]. Dtsch Med Wochenschr. 2013 Apr;138 Suppl 1:S6-15. PMID: 23529570.
Non-English language

Nauck M, Del Prato S, Rohwedder K, et al. Dapagliflozin vs glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin: 52-week results of a double-blind, randomised, controlled trial. Diabetologia. 2010;53((Nauck M.) Diabetes Centre, Bad Lauterberg, Germany):S107.
Meeting abstract

Nauck M, Hermansen K, Frid A, et al. Liraglutide, a once-daily human GLP-1 analogue, in type 2 diabetes provides similar glycaemic control with reduced body weight compared with glimepiride when added to metformin. Journal of Diabetes. 2009;1((Nauck M.) Diabeteszentrum Bad Lauterberg, Diabetologe (DDG), Bad Lauterberg im Harz, Germany):A21.
Meeting abstract

Nauck M, Weinstock R, Umpierrez G, et al. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes (award-5). Canadian Journal of Diabetes. 2013;37((Nauck M.; Weinstock R.; Umpierrez G.; Guerci B.; Boleyn K.; Skrivanek Z.; Milicevic Z.) Bad Lauterberg, Germany; Syracuse, NY USA; Atlanta, GA USA; Vandoeuvre les Nancy, France; Indianapolis, IN USA; Vienna, Austria):S44.
Meeting abstract

Nauck M, Weinstock RS, Umpierrez GE, et al. Efficacy and Safety of Dulaglutide Versus Sitagliptin After 52 Weeks in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-5). Diabetes Care 2014;37:2149-2158. Diabetes Care. 2015 Mar;38(3):538. PMID: 25715416.
No original data

Nauck MA, Petrie JR, Sesti G, et al. The once-weekly human GLP-1 analogue semaglutide provides significant reductions in HbA1c and body weight in patients with type 2 diabetes. Diabetologia. 2012;55((Nauck M.A.) Diabetes Centre, Bad Lauterberg im Harz, Germany):S7.
Meeting abstract

Nauck MA, Weinstock RS, Umpierrez G, et al. Efficacy and safety of dulaglutide vs sitagliptin after 52 weeks in type 2 diabetes (AWARD5). Diabetologia. 2013;56((Nauck M.A.) Diabetes Centre, Bad Lauterberg im Harz, Germany):S368.
Meeting abstract

Nauck MA, Weinstock RS, Umpierrez GE, et al. Efficacy and safety of dulaglutide vs. Sitagliptin after 52 weeks in type 2 diabetes (AWARD-5). Diabetes. 2013;62((Nauck M.A.; Weinstock R.S.; Umpierrez G.E.; Guerci B.; Boleyn K.; Skrivanek Z.; Milicevic Z.) Bad Lauterberg, Germany, Syracuse, NY, Atlanta, GA, Nancy, France, Indianapolis, IN, Vienna, Austria):A18.
Meeting abstract

Nauck M, Weinstock RS, Umpierrez GE, et al. Erratum: efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care

2014;37:2149-2158. Diabetes Care. 2015 Mar;38(3):538. PMID: 25715416.
No original data

Nct. A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects With Type 2 Diabetes With Inadequately Controlled Hypertension on an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB). ClinicalTrials.gov [http://clinicaltrials.gov]; 2010.
No original data

Nct. A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Blood Pressure Reduction With Ambulatory Blood Pressure Monitoring (ABPM), Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Hypertension and Type 2 Diabetes Mellitus. ClinicalTrials.gov [http://clinicaltrials.gov]; 2013.
No original data

Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)--a randomized placebo-controlled trial. Am Heart J. 2013 Aug;166(2):217-23 e11. PMID: 23895803.
No outcome of interest

Neeland I, McGuire DK, Chilton RJ, et al. The sodium glucose co-transporter 2 inhibitor (sglt2i) empagliflozin reduces weight and markers of visceral adiposity (VA) in type 2 diabetes (T2D) in short-and intermediate term. Circulation. 2014;130((Neeland I.; McGuire D.K.) Div of Cardiology, Univ of Texas, Southwestern Med Cntr, Dallas, United States).
Meeting abstract

Nerla R, Pitocco D, Zaccardi F, et al. Effect of pioglitazone on systemic inflammation is independent of metabolic control and cardiac autonomic function in patients with type 2 diabetes. Acta Diabetol. 2010 Dec;47 Suppl 1:117-22. PMID: 19787290.
Background medications

Neumann A, Weill A, Ricordeau P, et al. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. Diabetologia. 2012 Jul;55(7):1953-62. PMID: 22460763.
No drug comparison of interest

Neutel JM, Zhao C, Karyekar CS. Adding Saxagliptin to Metformin Extended Release (XR) or Uptitration of Metformin XR: Efficacy on Daily Glucose Measures. Diabetes Ther. 2013 Dec;4(2):269-83. PMID: 23881432.
Follow-up less than 3 months

Nevadunsky N, VanArsdale A, Kaur G, et al. Use of metformin is associated with improved endometrial cancer survival. Gynecologic Oncology. 2013;130(1):e74-e5.
Meeting abstract

Newman J, McGill JB, Patel S, et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment. Diabetologia. 2011;54((Newman J.) Boehringer Ingelheim, Ridgefield, United States):S333.
Meeting abstract

Ng JM, Mellor DD, Masson EA, et al. Sulphonyurea as a cause of severe hypoglycaemia in the community. Prim Care Diabetes. 2010 Apr;4(1):61-3. PMID: 20064751.

Background medications; No drug comparison of interest

Nicholls SJ, Tuzcu EM, Wolski K, et al. Lowering the triglyceride/high-density lipoprotein cholesterol ratio is associated with the beneficial impact of pioglitazone on progression of coronary atherosclerosis in diabetic patients: insights from the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) study. J Am Coll Cardiol. 2011 Jan 11;57(2):153-9. PMID: 21211686.
Background medications

Nichols GA, Conner C, Brown JB. Primary failure and initial success of metformin monotherapy in clinical practice. Diabetes. 2009;58((Nichols G.A.; Conner C.; Brown J.B.)).
Meeting abstract

Nicolle LE, Capuano G, Fung A, et al. Urinary tract infection (UTI) With canagliflozin (CANA) in subjects with type 2 diabetes mellitus (T2DM). Diabetes. 2013;62((Nicolle L.E.; Capuano G.; Fung A.; Usiskin K.) Winnipeg, MB, Canada, Raritan, NJ):A296.
Meeting abstract

Nieto J, Yale JF, Bakris G, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes mellitus and chronic kidney disease over 52 weeks. Diabetologia. 2013;56((Nieto J.) Hospital General Universitario, Ciudad Real, Spain):S381.
Meeting abstract

Nils E, Schioler L, Svensson AM, et al. Metformin and other glucose-lowering treatments: Risks and benefits. Nationwide epidemiological study. Diabetologia. 2012;55((Nils E.; Eeg-Olofsson K.; Gudbjornsdottir S.; Eliasson B.) Department of Medicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden):S27.
Meeting abstract

Ning G, Hong J, Zhang Y. Effect of anti-diabetic drugs on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes. 2012;61((Ning G.; Hong J.; Zhang Y.) Shanghai, China):A238.
Meeting abstract

Nino AJ, Bilezikian J, Borges J, et al. Effects of RSG/MET FDC on glycaemic control and BMD after 80 weeks of treatment in drug-naive type 2 diabetes mellitus subjects. Diabetologia. 2010;53((Nino A.J.; Adams P.L.; Jones A.R.; Acusta A.; Cobitz A.) MDC CVM, GlaxoSmithKline, King of Prussia, United States):S359.
Meeting abstract

Nishikawa K, Yanagawa T, Akiyama T, et al. The effect of sitagliptin on glycemic control, adiponectin and lipid metabolism. Diabetes. 2012;61((Nishikawa K.; Yanagawa T.; Akiyama T.; Kimura Y.; Morinaga R.) Tokyo, Japan):A706.
Meeting abstract

Niskanen L, Cefalu WT, Leiter LA, et al. Efficacy and safety of canagliflozin, a sodium glucose co-transporter 2 inhibitor, compared with glimepiride in patients with type 2 diabetes on background metformin. Diabetologia. 2012;55((Niskanen L.) Central Hospital Central Finland, Jyvaskyla, Finland):S314.
Meeting abstract

Niswender K, Pi-Sunyer X, Buse J, et al. Weight change with liraglutide and comparator therapies: an analysis of seven phase 3 trials from the liraglutide diabetes development programme. Diabetes Obes

Metab. 2013 Jan;15(1):42-54. PMID: 22862847.
Handsearch

Nitta Y, Tahara N, Honda A, et al. Effects of pioglitazone on coronary arterial inflammation evaluated by serial FDG-PET/CT in patients with impaired glucose tolerant or type 2 diabetes. Circulation. 2012;126(21).
Meeting abstract

Nitta Y, Tahara N, Tahara A, et al. Pioglitazone decreases coronary artery inflammation in impaired glucose tolerance and diabetes mellitus: evaluation by FDG-PET/CT imaging. JACC Cardiovasc Imaging. 2013 Nov;6(11):1172-82. PMID: 24229770.
Background medications; No type 2 diabetes

Nomoto H, Miyoshi H, Nakamura A, et al. A comparison of the effects of the DPP-4 inhibitor sitagliptin and the sulfonylurea glimepiride on metabolic parameters and endothelial function. Diabetologia. 2014;57(1):S355-S6.
Meeting abstract

Noriega J, Botros F, Threlkeld R, et al. The impact of LY2189265 (GLP-1 analog) on glycemic control in hispanic and non-hispanic caucasians with uncontrolled type 2 diabetes: An ego study analysis. Journal of Investigative Medicine. 2010;58(4):644.
Meeting abstract

Nowicki M, Rychlik I, Haller H, et al. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study. Int J Clin Pract. 2011 Dec;65(12):1230-9. PMID: 21977965.
Placebo-controlled trial; Background medications

Nowicki M, Rychlik I, Haller H, et al. Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment. Diabetes Obes Metab. 2011 Jun;13(6):523-32. PMID: 21332627.
Background medications; Comorbidity

Nyeland ME, Ploug UJ, Richards A, et al. Evaluation of the effectiveness of liraglutide and sitagliptin in type 2 diabetes: a retrospective study in UK primary care. Int J Clin Pract. 2015 Mar;69(3):281-91. PMID: 25302822.
Does not report long-term outcomes or adverse events

Nyeland ME, Ploug UJ, Skovgaard R, et al. Comparative effectiveness of liraglutide versus sitagliptin in type 2 diabetes in the United Kingdom: A retrospective study in primary care. Value in Health. 2013;16(7):A431.
Meeting abstract

Nyirjesy P, Sobel JD, Fung A, et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. Curr Med Res Opin. 2014 Jun;30(6):1109-19. PMID: 24517339.
No drug comparison of interest

Obeid R, Herrmann W, Jung J, et al. Metformin treatment is associated with lower vitamin B12 in serum without any evidence for intracellular B12 deficiency. Clinical Chemistry and Laboratory Medicine. 2012;50(9):A243.
Meeting abstract

Oguz A, Benroubi M, Brismar K, et al. Clinical outcomes after 24 months of insulin therapy in patients with type 2 diabetes in five countries: Results from the TREAT study. Current Medical Research and Opinion. 2013;29(8):911-20.
No drug comparison of interest; Background medications

Ohi K, Hayashi N. Efficacy and safety of linagliptin in patients with type 2 diabetes inadequately controlled by metformin. Japanese Pharmacology and Therapeutics. 2014;42(2):125-31.
Non-English language

Ohira M, Yamaguchi T, Ban N, et al. Pioglitazone improved cardio-ankle vascular index (CAVI) in type 2 diabetes patients through reducing oxidative stress. Journal of Diabetes. 2011;3((Ohira M.; Yamaguchi T.; Ban N.; Kawana H.; Nagayama D.; Nagumo A.; Endo K.; Saiki A.; Oyama T.; Miyashita Y.) Center of Diabetes, Endocrine and Metabolism, Sakura, Japan):267.
Meeting abstract

Ohira M, Yamaguchi T, Saiki A, et al. Pioglitazone improves the cardio-ankle vascular index in patients with type 2 diabetes mellitus treated with metformin. Diabetes Metab Syndr Obes. 2014;7:313-9. PMID: 25092992.
No outcome of interest

Ohki T, Akihiro I, Ooga T, et al. The effectiveness of liraglutide in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus compared to sitagliptin and pioglitazone. Hepatology. 2012;56((Ohki T.; Ooga T.; Sato K.; Fujiwara H.; Seki M.; Toda N.; Tagawa K.) Gastroenterology, Mitsui Memorial Hospital, Tokyo, Japan):906A.
Meeting abstract

Ohki T, Isogawa A, Iwamoto M, et al. The effectiveness of liraglutide in nonalcoholic fatty liver disease patients with type 2 diabetes mellitus compared to sitagliptin and pioglitazone. ScientificWorldJournal. 2012;2012:496453. PMID: 22927782.
Background medications

Ohki T, Isogawa A, Takeda T, et al. The effectiveness of glucagon like peptide 1 analogue in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus compared to dipeptidyl peptidase-4 inhibitor. Hepatology International. 2012;6(1):47.
Meeting abstract

Ohki T, Isogawa A, Takeda T, et al. The effectiveness of glucagon like peptide 1 analogue in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus compared to pioglitazone. Hepatology International. 2012;6(1):289.
Meeting abstract

Ohmura T, Hayashi N, Encinas J. [Pharmacological and clinical profiles of the DPP-4 inhibitor linagliptin (Trazenta)]. Nihon Yakurigaku Zasshi. 2012 Apr;139(4):174-83. PMID: 22498683.
No original data; No drug comparison of interest

Oishi M, Yamazaki K, Okuguchi F, et al. Changes in oral antidiabetic prescriptions and improved glycemic control during the years 2002-2011 in Japan (JDDM32). Journal of Diabetes Investigation. 2013((Oishi M., oishi108@mbox.kyoto-inet.or.jp) Oishi Clinic Kyoto Japan).
Okada K, Kotani K, Yagyu H, et al. Effects of treatment with liraglutide on oxidative stress and cardiac natriuretic peptide levels in patients with type 2 diabetes mellitus. Endocrine. 2014 Apr 3PMID: 24696097.
Does not meet study design criteria

Okahata S, Sakamoto K, Mitsumatsu T, et al. Evolving manners of a DPP4 inhibitor alogliptin (ALO) action on japanese diabetes patiens along with continuous administration. Diabetes. 2013;62((Okahata S.; Sakamoto K.; Mitsumatsu T.; Shiba T.) Tokyo, Japan):A667.
Meeting abstract

Okura H, Takagi T, Toda I. Pioglitazone affects left ventricular filling pressure in patients with ischemic heart disease and type 2 diabetes who underwent coronary intervention: An echo doppler sub-analysis from the prevention of in-stent neointimal proliferation by pioglitazone study (POPPS). Journal of the American College of Cardiology. 2010;55(10):A16.E150.
Meeting abstract

Olansky L, Reasner CA, Seck T, et al. A strategy implementing initial therapy with a fixed-dose combination tablet of sitagliptin and metformin in patients with type 2 diabetes provides superior glycaemic control compared with a strategy using initial metformin monotherapy over 44 weeks. Canadian Journal of Diabetes. 2009;33(3):208-9.
Meeting abstract

Ommen ES, Xu L, O'Neill EA, et al. Comparison of Treatment with Sitagliptin or Sulfonylurea in Patients with Type 2 Diabetes Mellitus and Mild Renal Impairment: A Post Hoc Analysis of Clinical Trials. Diabetes Ther. 2015 Jan 30PMID: 25633134.
No drug comparison of interest

Once-weekly exenatide more effective in glycaemic control than twice-daily. Australian Journal of Pharmacy. 2009;90(1067):79.
Meeting abstract

Onishi Y, Koshiyama H, Imaoka T, et al. Safety of exenatide once weekly for 52 weeks in Japanese patients with type 2 diabetes mellitus. J Diabetes Investig. 2013 Mar 18;4(2):182-9. PMID: 24843650.
No drug comparison of interest

Oppong BA, Pharmer LA, Oskar S, et al. The effect of metformin on breast cancer outcomes in patients with type 2 diabetes. Cancer Med. 2014 Jun 18PMID: 24944108.
Background medications; Comorbidity

Origasa H, Lee SH, Nakagawa H, et al. Pioglitazone use and bladder cancer - Hospital-based results from a nested case-control study in japan. Japanese Pharmacology and Therapeutics. 2013;41(7):663-7.
No drug comparison of interest

Ostenson CG, Matthaei S, Reaney M, et al. Treatment outcomes after initiation of exenatide twice daily or insulin in clinical practice: 12-month results from CHOICE in six European countries. Diabetes Metab Syndr Obes. 2013;6:171-85. PMID: 23667315.
Background medications; No drug comparison of interest

Ott C, Raff U, Schmidt S, et al. Effects of saxagliptin on early microvascular changes in patients with type 2 diabetes. Cardiovasc Diabetol. 2014;13:19. PMID: 24423149.
Follow-up less than 3 months; Does not meet study design criteria

Ou HT, Chen YT. Comparativeeffectivenessresearch ofmetformin-based oral hypoglycemic therapy in taiwan's population-based database. Pharmacoepidemiology and Drug Safety. 2014;23((Ou H.-T.; Chen Y.-T.) Institute of Clinical Pharmacy and

Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan):241-2.
Meeting abstract

Pala S, Esen O, Akcakoyun M, et al. Rosiglitazone, but not pioglitazone, improves myocardial systolic function in type 2 diabetic patients: a tissue Doppler study. Echocardiography. 2010 May;27(5):512-8. PMID: 20412274.
Background medications

Pan C, Han P, Ji Q, et al. Efficacy and safety of alogliptin in subjects with type 2 diabetes: A multicenter, randomized, double-blind, placebo-controlled, phase 3 study in mainland China, Taiwan and Hong Kong. Diabetes. 2013;62((Pan C.; Han P.; Ji Q.; Li C.; Lu J.; Yang J.; Li W.; Zeng J.; Chan J.; Hsieh A.-T.) Beijing, China, Shenyang, China, Xi'an, China, Hangzhou, China, Wuhan, China, Sha Tin, Hong Kong, Taipei, Taiwan):A299.
Meeting abstract

Pan CY, Li WH, Zeng JE, et al. [The design and baseline characteristics of a phase III study to evaluate the efficacy and safety of alogliptin versus placebo in type 2 diabetes mellitus in Mainland China]. Zhonghua Nei Ke Za Zhi. 2013 Nov;52(11):932-5. PMID: 24439186.
Non-English language

Pan CY, Yang W, Tou C, et al. Efficacy and safety of saxagliptin in drug-naive Asian patients with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Metab Res Rev. 2012 Mar;28(3):268-75. PMID: 22081481.
Placebo-controlled trial- No drug comparison of interest

Panda A, Panigrahi M, Pradhan S, et al. Influence of different oral anti-diabetic drugs on health related quality of life in Type 2 Diabetes Mellitus patients. Biomedicine (India). 2014;34(4):468-73.
Follow-up less than 3 months; Backgroundmedications

Pandya BJ, Bron M, McCall T, et al. Achieving glycemic goal with initial versus sequential combination therapy using metformin and pioglitazone in type 2 diabetes mellitus. Curr Med Res Opin. 2011 Jan;27(1):189-95. PMID: 21142610.
No drug comparison of interest; Does not meet study design criteria

Pantalone KM, Kattan MW, Yu C, et al. Increased risk of overall mortality in patients with type 2 diabetes receiving glipizide, Glyburide, and Glimepiride vs. Metformin. A Retrospective Analysis. Endocrine Reviews. 2012;33(3).
Meeting abstract

Pantalone KM, Kattan MW, Yu C, et al. The risk of overall mortality in patients with Type 2 diabetes receiving different combinations of sulfonylureas and metformin: a retrospective analysis. Diabet Med. 2012 Aug;29(8):1029-35. PMID: 22248043.
No drug comparison of interest

Pantalone KM, Kattan MW, Yu C, et al. The risk of overall mortality in patients with type 2 diabetes receiving different combinations of sulfonylureas and metformin: A retrospective analysis. Endocrine Reviews. 2011;32(3).
Meeting abstract

Parikh S, Hardy E, Wei L, et al. Dapagliflozin improves glycaemic control and reduces body weight across various patient populations with type 2 diabetes mellitus. Diabetologia. 2012;55((Parikh S.; Hardy E.) AstraZeneca, Wilmington, United States):S305.

Meeting abstract

Parikh SJ, Ingelgard A, Langkilde AM, et al. Weight loss related quality of life among type 2 diabetes mellitus patients treated with dapagliflozin. Diabetologia. 2013;56((Parikh S.J.; Sugg J.; Grandy S.) AstraZeneca LP, Wilmington, United States):S376-S7.
Meeting abstract

Patel S, Heise T, Larbig M, et al. The dipeptidyl peptidase (DPP)-4 inhibitor linagliptin improves (beta)-cell function and postprandial glucose in type 2 diabetes (T2D). Diabetes. 2013;62((Patel S.; Heise T.; Larbig M.; Weber S.; Seck T.; Hehnke U.; Woerle H.J.; Dugi K.) Bracknell, United Kingdom, Neuss, Germany, Ingelheim, Germany):A296.
Meeting abstract

Patel S, Schernthaner G, Barnett AH, et al. Renal safety of linagliptin in elderly patients with type 2 diabetes: Analysis of pooled patient data from 7 phase 3 clinical trials. Diabetologia. 2013;56((Patel S.) Boehringer Ingelheim, Bracknell, United Kingdom):S370.
Meeting abstract

Patel S, Schernthaner G, Barnett AH, et al. Safety and efficacy of linagliptin in elderly patients with type 2 diabetes: Evidence from 1331 individuals aged (greater-than or equal to)65 years. Diabetologia. 2012;55((Patel S.) Boehringer Ingelheim Ltd, Bracknell, United Kingdom):S351.
Meeting abstract

Patel S, Von Eynatten M, Weber S, et al. Linagliptin improves glycaemic control in type 2 diabetes mellitus (T2DM) patients with increased cardiovascular (CV) risk. Diabetes, Stoffwechsel und Herz. 2011;20(6):431.
Meeting abstract

Patel S, Weber S, Emser A, et al. Linagliptin improves glycaemic control independently of diabetes duration and insulin resistance in patients with type 2 diabetes. Diabetologia. 2011;54((Patel S.) Boehringer Ingelheim, Bracknell, United Kingdom):S339.
Meeting abstract

Paul S, Best J, Klein K, et al. Effects of HbA1c and weight reduction on blood pressure in patients with type 2 diabetes mellitus treated with exenatide*. Diabetes Obes Metab. 2012 Sep;14(9):826-34. PMID: 22510305.
Does not apply; No drug comparison of interest

Paul S, Best JH, Klein K, et al. Glycemic and weight lowering effects of exenatide once weekly are associated with blood pressure changes in patients with type 2 diabetes. Diabetes. 2011;60((Paul S.; Best J.H.; Klein K.; Han J.; Maggs D.) Brisbane, Australia):A296.
Meeting abstract

Paulus JK, Cossor FI, Williams CD, et al. Metformin (M), diabetes (DM), and colorectal cancer (CRC) survival among U.S. Veterans. Journal of Clinical Oncology. 2014;32(15).
Meeting abstract

Pavlicek V. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin. [German]. Diabetologe; 2011. p. 37-8.
No original data

Pawaskar M, Bonafede M, Johnson BH, et al. Time to treatment modification among patients with Type 2 diabetes who initiated exenatide twice daily or insulin glargine. Diabetic Medicine. 2011;28((Pawaskar M.;

Hoogwerf B.) Eli Lilly and Company, Indianapolis, United States):72.
Meeting abstract

Pawaskar M, Li Q, Hoogwerf BJ, et al. Metabolic outcomes of matched patient populations initiating exenatide BID vs. insulin glargine in an ambulatory care setting. Diabetes Obes Metab. 2012 Jul;14(7):626-33. PMID: 22321776.
No drug comparison of interest; Background medications

Pawaskar M, Li Q. Clinical outcomes of elderly patients initiating exenatide twice daily compared to insulin glargine. Diabetes. 2012;61((Pawaskar M.) Indianapolis, United States):A608-A9.
Meeting abstract

Pawaskar M, Tuttle KR, Li Q, et al. Observational study of kidney function and albuminuria in patients with type 2 diabetes treated with exenatide BID versus insulin glargine. Ann Pharmacother. 2014 May;48(5):571-6. PMID: 24497624.
Background medications

Pawaskar M, Zagar A, Sugihara T, et al. Healthcare resource utilization and costs assessment of type 2 diabetes patients initiating exenatide BID or glargine: a retrospective database analysis. J Med Econ. 2011;14(1):16-27. PMID: 21158486.
Background medications; No outcome of interest

Pencek R, Anderson PW, Blickensderfer A, et al. Exenatide twice daily: A retrospective analysis of pooled exenatide clinical trial efficacy data stratified by race, age, duration of diabetes, BMI and gender. Diabetologia. 2011;54((Pencek R.; Blickensderfer A.; Li Y.; Brunell S.) Amylin Pharmacehticals, Inc., San Diego, United States):S313.
Meeting abstract

Pencek R, Blickensderfer A, Li Y, et al. Exenatide once weekly for the treatment of type 2 diabetes: effectiveness and tolerability in patient subpopulations. Int J Clin Pract. 2012 Nov;66(11):1021-32. PMID: 22925173.
No drug comparison of interest

Pencek R, Blickensderfer A, Li Y, et al. Exenatide twice daily: analysis of effectiveness and safety data stratified by age, sex, race, duration of diabetes, and body mass index. Postgrad Med. 2012 Jul;124(4):21-32. PMID: 22913891.
Background medications

Pencek R, Brunell SC, Li Y, et al. Exenatide once weekly for the treatment of type 2 diabetes mellitus: clinical results in subgroups of patients using different concomitant medications. Postgrad Med. 2012 Jul;124(4):33-40. PMID: 22913892.
Background medications

Pencek R, Brunell SC, Li Y, et al. Use of concomitant glucose-lowering therapies and associated treatment results observed in clinical trials of twice-daily exenatide. Endocr Pract. 2012 Mar-Apr;18(2):227-37. PMID: 22446132.
Background medications

Pendergrass M, Fenton C, Haffner SM, et al. Exenatide and sitagliptin are not associated with increased risk of acute renal failure: a retrospective claims analysis. Diabetes Obes Metab. 2012 Jul;14(7):596-600. PMID: 22268550.
Background medications

Penfornis A, Bourdel-Marchasson I, Quere S, et al. Real life evaluation of DPP4-inhibitors versus other oral antidiabetics in elderly patients with type 2 diabetes mellitus treated with metformin: Results from the

HYPOCRAS study. Diabetologia. 2012;55((Penfornis A.) University of Franche-Comte, CHU of Besancnullon, Rueil Malmaison, France):S349.
Meeting abstract

Penfornis A, Bourdel-Marchasson I, Quere S, et al. Real-life comparison of DPP4-inhibitors with conventional oral antidiabetics as add-on therapy to metformin in elderly patients with type 2 diabetes: the HYPOCRAS study. Diabetes Metab. 2012 Dec;38(6):550-7. PMID: 22996038.
No drug comparison of interest

Penfornis A, Bourdel-Marchasson I, Quere S, et al. Real-life comparison of DPP4-inhibitors with conventional oral antidiabetics as add-on therapy to metformin in elderly patients with type 2 diabetes: The HYPOCRAS study. Medecine des Maladies Metaboliques. 2014;8(1):47-55.
No drug comparison of interest

Penno G, Pucci L, Lucchesi D, et al. Effects of pioglitazone on endothelial function in type 2 diabetic patients with vascular complications: The splendor study. Diabetes. 2013;62((Penno G.; Pucci L.; Lucchesi D.; Bruno R.; Russo E.; Garofolo M.; Bornez V.S.; Russo R.; De Kreutzenberg S.; Miccoli R.; Avogaro A.; Ghiadoni L.; Di Pietro C.; Del Prato S.) Pisa, Italy, Padova, Italy, Rome, Italy):A129.
Meeting abstract

Perciaccante A, Balbi M, Casarin P, et al. Increased risk of hepatocellular carcinoma and therapy of type 2 diabetes mellitus. Journal of Hepatology. 2009;50((Perciaccante A., antonioperciaccante@libero.it; Balbi M.; Casarin P.; Donadon V.) Department of Medicine, Internal Medicine 3rd, Pordenone Hospital, Pordenone, Italy):S296.
Meeting abstract

Perez A, Franch J, Cases A, et al. [Relationship between the degree of glycemic control and diabetes characteristics and hyperglycemia treatment in type 2 diabetes. DIABES Study]. Med Clin (Barc). 2012 May 5;138(12):505-11. PMID: 22118974.
Non-English language

Perez A, Zhao Z, Spanheimer R. Effect of pioglitazone and metformin fixed-dose combination on biomarkers of inflammation and dyslipidemia in patients with type 2 diabetes. Canadian Journal of Diabetes. 2009;33(3):246.
Meeting abstract

Perez A, Zhao Z, Spanheimer R. Effect of pioglitazone and metformin fixed-dose combination on hs-CRP and adiponectin in patients with type 2 diabetes. Diabetes. 2009;58((Perez A.; Zhao Z.; Spanheimer R.) Deerfield, United States).
Meeting abstract

Perez-Cadena Z, Daniele G, Chavez A, et al. Low-dose (15 mg/day) pioglitazone improves glycemic control and insulin secretion/insulin sensitivity index with minimal weight gain in type 2 diabetes. Endocrine Reviews. 2012;33(3).
Meeting abstract

Perez-Cadena Z, Daniele G, Chavez A, et al. Low-dose (15 mg/day) pioglitazone treatment improves glycemic control, and whole-body and adipocyte insulin resistance with minimal weight gain in type 2 diabetic subjects. Diabetes. 2012;61((Perez-Cadena Z.; Daniele G.; Chavez A.; Kamath S.; Zuo P.; Chang Z.; Andreozzi F.; Paez A.; Winnier D.; Arya R.; Hansis-Diarte A.; Cortez L.; Jenkinson C.; Fanti P.; Gastaldelli

A.; Defronzo R.; Tripathy D.; Folli F.) San Antonio, United States):A281.
Meeting abstract

Perez-Monteverd A, Seck T, Xu L, et al. Efficacy and safety of sitagliptin and the fixed-dose combination of sitagliptin and metformin versus pioglitazone in drug-naive patients with type 2 diabetes. Diabetologia. 2010;53((Perez-Monteverd A.) Centro Medico Docente La Trinidad, Caracas, Bolivarian, Venezuela):S325-S6.
Meeting abstract

Peters KE, Chubb SA, Davis WA, et al. The relationship between hypomagnesemia, metformin therapy and cardiovascular disease complicating type 2 diabetes: the Fremantle Diabetes Study. PLoS One. 2013;8(9):e74355. PMID: 24019966.
Does not apply

Petrica L, Petrica M, Vlad A, et al. Does PPARg-agonist rosiglitazone exert nephro- and neuroprotective effects in normoalbuminuric type 2 diabetes mellitus patients? Journal of the Neurological Sciences. 2009;285((Petrica L.; Gluhovschi G.; Gluhovschi C.; Bob F.; Jianu C.D.; Gadalean F.; Velciov S.; Trandafirescu V.; Marian R.) Neurology, University of Medicine and Pharmacy, Timisoara, Romania):S169.
Meeting abstract

Petrica M, Petrica L, Vlad A, et al. Neuro- and renoprotective effects of pioglitazone versus glimepiride in normoalbuminuric patients with type-2 diabetes mellitus: A randomized controlled trial. European Journal of Neurology. 2012;19((Petrica M.) Neurology, Victor Babes University of Medicine, County Emergency Hospital, Timisoara, Romania):493.
Meeting abstract

Pfister R, Cairns R, Erdmann E, et al. A clinical risk score for heart failure in patients with type 2 diabetes and macrovascular disease: an analysis of the PROactive study. Int J Cardiol. 2013 Jan 10;162(2):112-6. PMID: 21636144.
Placebo-controlled trial; Background medications

Pfutzner A, Forst T. Elevated intact proinsulin levels are indicative of Beta-cell dysfunction, insulin resistance, and cardiovascular risk: impact of the antidiabetic agent pioglitazone. J Diabetes Sci Technol. 2011 May;5(3):784-93. PMID: 21722594.
No original data; No outcome of interest

Pfutzner A, Forst T. Impact of oral antidiabetic drugs on a biomarker panel concept for treatment selection and monitoring in patients with type 2 diabetes. Journal of Diabetes Science and Technology. 2012;6(2):A144-A5.
Meeting abstract

Pfutzner A, Gurieva I, Antsiferov M, et al. Saxagliptin either as add-on therapy to metformin or as initial combination therapy with metformin improves glycaemic control in patients with type 2 diabetes. Endocrine Abstracts. 2010;20((Pfutzner A.) Institute for Clinical Research and Development, Mainz, Germany):P359.
Meeting abstract

Pfutzner AH, Schorsch A, Forst T, et al. Metformin/saxagliptin combination therapy can replace insulin therapy in patients with type 2 diabetes: Interim results from the SAXAswitch study. Diabetologia. 2011;54((Pfutzner A.H.; Forst T.; Pfutzner A.) R and D, IKFE Institute for Clinical Research and Development, Mainz, Germany):S338.
Meeting abstract

Phey Ming Y, Lockman KA, Elton R, et al. Comparison of the effects of long-term pioglitazone and rosiglitazone therapy on liver enzymes in type 2 diabetes. British Journal of Diabetes and Vascular Disease. 2011;11(3):121-9.
Background medications; No outcome of interest

Philis-Tsimikas A, Del Prato S, Satman I, et al. Insulin degludec is superior to sitagliptin in improving glycemic control in insulin-naive patients with type 2 diabetes. Diabetes. 2012;61((Philis-Tsimikas A.; Del Prato S.; Satman I.; Bhargava A.; Dharmalingam M.; Skjoth T.V.; Rasmussen S.; Garber A.J.) San Diego, United States):A263.
Meeting abstract

Pirags V, El Damassy H, Dabrowski M, et al. Low risk of severe hypoglycaemia in patients with type 2 diabetes mellitus starting insulin therapy with premixed insulin analogues BID in outpatient settings. International Journal of Clinical Practice. 2012;66(11):1033-41.
Background medications; No drug comparison of interest

Pistrosch F, Herbrig K, Passauer J, et al. Influence of rosiglitazone on proteinuria and renal haemodynamic in type 2 diabetic patients with overt diabetic nephropathy. Diabetologia. 2010;53((Pistrosch F.; Herbrig K.; Passauer J.; Gross P.) Nephrology, Dept of Medicine, University Hospital, Dresden, Germany):S484.
Meeting abstract

Pistrosch F, Passauer J, Herbrig K, et al. Effect of thiazolidinedione treatment on proteinuria and renal hemodynamic in type 2 diabetic patients with overt nephropathy. Horm Metab Res. 2012 Nov;44(12):914-8. PMID: 22723267.
Background medications

Polidori D, Mari A, Ferrannini E. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, improves model-based indices of beta cell function in patients with type 2 diabetes. Diabetologia. 2014 May;57(5):891-901. PMID: 24585202.
No drug comparison of interest

Polidori D, Sanghvi A, Seeley R, et al. Predicted temporal changes in energy intake and energy expenditure in subjects with type 2 diabetes treated with canagliflozin. Diabetologia. 2014;57(1):S331-S2.
Meeting abstract

Polidori D, Zhao Y, Alba M, et al. Treatment with canagliflozin (CANA), a sodium glucose co-transporter 2 (SGLT2) inhibitor, for 26 weeks improves indices of betacell function (BCF). Diabetes. 2012;61((Polidori D.; Zhao Y.; Alba M.; Ferrannini E.) San Diego, United States):A265.
Meeting abstract

Pollack MF, Purayidathil FW, Bolge SC, et al. Patient-reported tolerability issues with oral antidiabetic agents: Associations with adherence; treatment satisfaction and health-related quality of life. Diabetes Research and Clinical Practice. 2010;87(2):204-10.
No drug comparison of interest; No outcome of interest

Polyzos SA, Zografou I, Karagianni P, et al. Exenatide versus insulin glargine in type 2 diabetes inadequately treated with metformin. Diabetes Technology and Therapeutics. 2015;17((Polyzos S.A.; Karagianni P.) 2nd Medical Clinic, Hippokration General Hospital, Thessaloniki, Greece):A49.

Meeting abstract

Ponzani P. Long-term effectiveness and safety of liraglutide in clinical practice. Minerva Endocrinol. 2013 Mar;38(1):103-12. PMID: 23435446.
Background medications; No drug comparison of interest

Pop-Busui R, Lombardero M, Lavis V, et al. Relation of severe coronary artery narrowing to insulin or thiazolidinedione use in patients with type 2 diabetes mellitus (from the Bypass Angioplasty Revascularization Investigation 2 Diabetes Study). Am J Cardiol. 2009 Jul 1;104(1):52-8. PMID: 19576321.
No drug comparison of interest

Portillo Sanchez P, Bril F, Lomonaco R, et al. Effects of extended pioglitazone treatment (PIO) on bone metabolism in patients with prediabetes and type 2 diabetes mellitus (T2DM). Diabetes. 2014;63((Portillo Sanchez P.; Bril F.; Lomonaco R.; Maximos M.; Bruder J.; Orsak B.; Hecht J.; Cusi K.) Gainesville, FL, San Antonio, TX):A293-A4.
Meeting abstract

Pottegard A, Bjerregaard BK, Larsen MD, et al. Use of exenatide and liraglutide in Denmark: A drug utilization study. European Journal of Clinical Pharmacology. 2014;70(2):205-14.
Background medications

Pradhan AD, Everett BM, Cook NR, et al. Effects of initiating insulin and metformin on glycemic control and inflammatory biomarkers among patients with type 2 diabetes: the LANCET randomized trial. JAMA. 2009 Sep 16;302(11):1186-94. PMID: 19755697.
Background medications

Pratley R, McCall T, Fleck P, et al. Alogliptin use in the elderly: A pooled analysis from phase 2-3 studies. Diabetes. 2009;58((Pratley R.; Mccall T.; Fleck P.; Wilson C.; Mekki Q.)).
Meeting abstract

Pratley R, Stewart M, Cirkel D, et al. HARMONY 4: 52-week efficacy of albiglutide vs insulin glargine in patients with type 2 diabetes mellitus. Diabetologia. 2013;56((Pratley R.) Florida Hospital Diabetes Institute, Sanford-Burnham Medical Research, Orlando, United States):S360-S1.
Meeting abstract

Pratley R, Wilson C, Fleck P. Alogliptin plus metformin combination therapy vs alogliptin or metformin monotherapy for type 2 diabetes mellitus. Diabetologia. 2012;55((Pratley R.) Florida Hospital Diabetes and Translational Research Institute and Sanford, Burnham Institute, Orlando, United States):S347-S8.
Meeting abstract

Pratley RE, Kipnes MS, Fleck PR, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy. Diabetes Obes Metab. 2009 Feb;11(2):167-76. PMID: 19125778.
No drug comparison of interest; Placebo-controlled trial

Pratley RE, McCall T, Fleck PR, et al. Alogliptin use in elderly people: a pooled analysis from phase 2 and 3 studies. J Am Geriatr Soc. 2009 Nov;57(11):2011-9. PMID: 19793357.
Background medications

Pratley RE, Reusch JE, Fleck PR, et al. Efficacy and safety of the dipeptidyl

peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin. 2009 Oct;25(10):2361-71. PMID: 19650752.
No drug comparison of interest

Prato S. Linagliptin for the treatment of type 2 diabetes. Expert Opin Pharmacother; 2011. p. 2759-62.
Placebo-controlled trial; No original data

Preston MA, Riis AH, Ehrenstein V, et al. Metformin use and prostate cancer risk. Journal of Urology. 2014;191(4):e831-e2.
Meeting abstract

Pscherer S, Larbig M, von Stritsky B, et al. In type 2 diabetes patients, insulin glargine is associated with lower postprandial release of intact proinsulin compared with sulfonylurea treatment. J Diabetes Sci Technol. 2012 May;6(3):634-40. PMID: 22768894.
Follow-up less than 3 months; No outcome of interest

Ptaszynska A, Chalamandaris AG, Sugg J, et al. Dapagliflozin does not impact renal function in patients with type 2 diabetes. Diabetologia. 2012;55((Ptaszynska A.; List J.F.) Bristol-Myers Squibb, Princeton, United States):S107.
Meeting abstract

Ptaszynska A, Johnsson K, Apanovitch AM, et al. Safety of dapagliflozin in clinical trials for type 2 diabetes mellitus. Internal Medicine Journal. 2013;43((Johnsson K.) AstraZeneca, Molndal, Sweden):50.
Meeting abstract

Ptaszynska A, Johnsson KM, Parikh SJ, et al. Safety profile of dapagliflozin for type 2 diabetes: pooled analysis of clinical studies for overall safety and rare events. Drug Saf. 2014 Oct;37(10):815-29. PMID: 25096959.
Does not account for confounding

Ptaszynska A, Mansfield T, Johnsson E, et al. Long-term renal safety with dapagliflozin treatment. Diabetologia. 2014;57(1):S322.
Meeting abstract

Ptaszynska A, Parikh S, Hardy E, et al. Dapagliflozin improves glycaemic control and reduces body weight across various patient populations with type 2 diabetes mellitus. Internal Medicine Journal. 2013;43((Parikh S.; Hardy E.) AstraZeneca, Wilmington, United States):49.
Meeting abstract

Pulcina A, Veronesi G, Bonfadini S, et al. Effects of medium-long term regular treatment with exenatide in type 2 diabetic patients: A lombard multicenter initiative. Giornale Italiano di Diabetologia e Metabolismo. 2013;33(2):61-7.
Background medications; No drug comparison of interest

Punthakee Z, Almeras N, Despres JP, et al. Impact of rosiglitazone on body composition, hepatic fat, fatty acids, adipokines and glucose in persons with impaired fasting glucose or impaired glucose tolerance: a sub-study of the DREAM trial. Diabet Med. 2014 Jun 3PMID: 24890138.
No type 2 diabetes; Placebo-controlled trial

Punthakee Z, Bosch J, Dagenais G, et al. Design, history and results of the Thiazolidinedione Intervention with vitamin D Evaluation (TIDE) randomised controlled trial. Diabetologia. 2012 Jan;55(1):36-45. PMID: 22038523.
No drug comparison of interest; Background medications

Qiu H, Rhoads GG, Berlin JA, et al. Initial metformin or sulphonylurea exposure and cancer occurrence among patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2013 Apr;15(4):349-57. PMID: 23137378.
Does not account for confounding

Quilliam BJ, Simeone JC, Ozbay AB. Risk factors for hypoglycemia-related hospitalization in patients with type 2 diabetes: a nested case-control study. Clin Ther. 2011 Nov;33(11):1781-91. PMID: 22018449.
Background medications; No drug comparison of interest

Rafeiro E, Ross SA, Meinicke T, et al. Efficacy and safety of 5 mg daily dosing regimens with linagliptin in patients with type 2 diabetes inadequately controlled on metformin. Diabetologia. 2011;54((Rafeiro E.) Boehringer Ingelheim, Burlington, Canada):S338-S9.
Meeting abstract

Ragonesi PD, Maffioli P, Cicero AFG, et al. Sitagliptin added to previously taken anti-diabetic agents on insulinresistance and lipid profile: A two years study evaluation. Diabetologia. 2012;55((Ragonesi P.D.) Diabetes Care Unit, S. Carlo Hospital, Milano, Italy):S342-S3.
Meeting abstract

Rahman IU, Malik SA, Bashir M, et al. Monotherapy with metformin or glimepiride and changes in serum sialic acid in type 2 diabetes mellitus. British Journal of Diabetes and Vascular Disease. 2011;11(3):137-40.
No outcome of interest

Rahman IU, Malik SA, Bashir M, et al. Serum sialic acid changes in type 2 diabetic patients on metformin or rosiglitazone treatment. J Clin Pharm Ther. 2010 Dec;35(6):685-90. PMID: 21054460.
Does not account for confounding; Does not meet study design criteria

Rajpathak S, Fu C, Brodovicz K, et al. Sulfonylureas associated with higher emergency room use in elderly with diabetes. Diabetes. 2013;62((Rajpathak S.; Fu C.; Brodovicz K.; Engel S.S.) North Wales, United States):A276.
Meeting abstract

Rajpathak SN, Fu C, Engel SS, et al. Sulfonylureas are associated with elevated risk of hip fractures among elderly men and women with type-2 diabetes. Value in Health. 2013;16(3):A11-A2.
Meeting abstract

Ramos-Coss M, Rodriguez-Rivera N, Molina-Guarneros JA, et al. Lack of therapeutic efficacy on type 2 diabetic patients treated with glibenclamide and metformin in Mexico city. Pharmacoepidemiology and Drug Safety. 2013;22((Ramos-Coss M.; Rodriguez-Rivera N.; Molina-Guarneros J.A.) Pharmacology, Universidad Nacional Autonoma de Mexico (UNAM), Mexico City, Mexico):488-9.
Meeting abstract

Raparla S, Wei W, Grabner M, et al. Real-world practice patterns, clinical and economic outcomes among us patients with type 2 diabetes initiating once-daily injectable pen therapy with insulin glargine or liraglutide. Journal of General Internal Medicine. 2012;27((Raparla S.; Grabner M.; Quimbo R.) HealthCore, Inc., Wilmington, United States):S293.
Meeting abstract

Rascati KL, Richards KM, Lopez D, et al. Progression to insulin for patients with

diabetes mellitus using the Texas Medicaid database. Clin Ther. 2011 Dec;33(12):2016-20. PMID: 22101160.
No outcome of interest

Rathmann W, Kostev K, Gruenberger JB, et al. Treatment persistence, hypoglycaemia and clinical outcomes in type 2 diabetes patients with dipeptidyl peptidase-4 inhibitors and sulphonylureas: a primary care database analysis. Diabetes Obes Metab. 2013 Jan;15(1):55-61. PMID: 22862879.
Background medications

Ratner R, Han J, Nicewarner D, et al. Cardiovascular safety of exenatide BID: an integrated analysis from controlled clinical trials in participants with type 2 diabetes. Cardiovasc Diabetol. 2011;10:22. PMID: 21410975.
No drug comparison of interest

Rauch T, Graefe-Mody U, Deacon CF, et al. Linagliptin increases incretin levels, lowers glucagon, and improves glycemic control in type 2 diabetes mellitus. Diabetes Therapy. 2012;3(1):1-14.
Follow-up less than 3 months; Placebo-controlled trial

Raval Amit D, Chovatiya K, Bhavsar Ankit B, et al. Dapagliflozin for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2011.
No original data

Ravichandran S, DeFronzo R, Garber AJ, et al. Once-daily saxagliptin added to metformin is well tolerated and provides sustained glycaemic control over 102 weeks in patients with type 2 diabetes. Diabetologia. 2009;52(S1):S60.
Meeting abstract

Raz I, Bhatt DL, Hirshberg B, et al. Incidence of Pancreatitis and Pancreatic Cancer in a Randomized Controlled Multicenter Trial (SAVOR-TIMI 53) of the Dipeptidyl Peptidase-4 (DPP-4) Inhibitor Saxagliptin. Diabetes Care. 2014 Jun 9PMID: 24914244.
Backgrouond medications; Placebo-controlled trial

Raz I, Cahn A, Scirica BM, et al. Predisposing factors for hypoglycemia: Analysis from the savortimi 53 trial. Diabetes. 2014;63((Raz I.; Cahn A.; Scirica B.M.; Eliaschewitz F.; Moses R.; Hirshberg B.; Sjostrand M.; Iqbal N.; Mosenzon O.; Lewis B.S.; Bhatt D.L.) Jerusalem, Israel, Boston, MA, Sao Paulo, Brazil, Sydney, Australia, Wilmington, DE, Molndal, Sweden, Princeton, NJ, Haifa, Israel):A66.
Meeting abstract

Raz I, Scirica BM, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes. Hypertension. 2014;63(6):e167.
Meeting abstract

Reaney M, Mitchell BD, Wang P, et al. Patient-reported outcomes with dulaglutide vs. metformin (AWARD-3). Diabetes. 2013;62((Reaney M.; Mitchell B.D.; Wang P.; Pechtner V.; Curtis B.; Van Brunt K.) Indianapolis, United States):A264.
Meeting abstract

Reaney M, Wang P, Lakshmanan M, et al. Patient-reported outcomes with dulaglutide, exenatide, or placebo (AWARD-1). Diabetes. 2013;62((Reaney M.; Wang P.; Lakshmanan M.; Van Brunt K.; Curtis B.; Mitchell B.) Indianapolis, United States):A265.
Meeting abstract

Reaney M, Yu M, Adetunji O, et al. Patient-reported outcomes (PRO) from a 104 week, phase 3, randomised, placebo-controlled study comparing once weekly dulaglutide to sitagliptin and placebo in metformin-treated patients with Type 2 diabetes; the Assessment of Weekly Administration of Dulaglutide in Diabetes (AWARD-5) trial. Diabetic Medicine. 2014;31((Reaney M.) Global Health Outcomes, Eli Lilly and Company, Windlesham, United Kingdom):50.
Meeting abstract

Reasner CA, Olansky L, Seck T, et al. Initial therapy with the Fixed-Dose Combination (FDC) of sitagliptin and metformin (JANUMET(trademark)) in patients with type 2 diabetes mellitus provides superior glycaemic control and HbA1c goal attainment with lower rates of abdominal pain and diarrhea vs metformin alone. Diabetologia. 2009;52(S1):S295.
Meeting abstract

Reasner CA, Olansky L, Seck TL, et al. Initial therapy with the fixed-dose combination (FDC) of sitagliptin and metformin (JANUMETTM) in patients with type 2 diabetes mellitus (T2DM) provides superior glycemic control and A1C goal attainment with lower rates of abdominal pain and diarrhea vs. metformin alone. Diabetes. 2009;58((Reasner C.A.; Olansky L.; Seck T.L.; Debora E.W.-H.; Luo E.; Chen M.; Reigle L.B.; Ling Y.; Amy O.J.-L.; Kaufman K.D.; Goldstein B.J.)).
Meeting abstract

Redaniel MT, Jeffreys M, May MT, et al. Associations of type 2 diabetes and diabetes treatment with breast cancer risk and mortality: a population-based cohort study among British women. Cancer Causes Control. 2012 Nov;23(11):1785-95. PMID: 22971998.
Does not account for confounding

Reinhardt R, Nauck MA, Stewart M, et al. HARMONY 2 results at week 52 primary endpoint: Once-weekly albiglutide monotherapy for patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetologia. 2013;56((Reinhardt R.; Stewart M.; Jones-Leone A.; Yang F.; Perry C.) GlaxoSmithKline, Upper Merion, United States):S360.
Meeting abstract

Rendell M, Chrysant S, Emser A, et al. Linagliptin effectively reduces HbA1c independent of age in patients with type 2 diabetes. Pharmacotherapy. 2011;31(10):337e-8e.
Meeting abstract

Rendell M, Chrysant S, Trujillo A, et al. Linagliptin improves glycemic control independent of body mass index in patients with type 2 diabetes. Journal of General Internal Medicine. 2011;26((Rendell M.) Creighton Diabetes Center, Omaha, United States):S214-S5.
Meeting abstract

Rendell M, Chrysant SG, Emser A, et al. Linagliptin effectively reduces blood glucose independent of age in patients with type 2 diabetes. Endocr Rev. 2011;32(3).
Rendell M, Chrysant SG, Emser A, et al. Linagliptin improves glycemic control independent of gender in patients with type 2 diabetes. Endocrine Reviews. 2011;32(3).
Meeting abstract

Rendell M, Chrysant SG. Review of the safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled study. Postgrad Med. 2011;123(4):183-6.

No original data

Retnakaran R, Kramer CK, Zinman B. Liraglutide and the preservation of pancreatic (beta)-cell function in early type 2 diabetes: The LIBRA trial. Diabetes care 2014;37:3270-3278. Diabetes Care. 2015;38(2):e26.
Placebo-controlled trial

Reusch J, Rosenstock J, Bush M, et al. A time course analysis of glycaemic improvements with albiglutide, a long-acting GLP-1-receptor agonist for the treatment of type 2 diabetes. Canadian Journal of Diabetes. 2009;33(3):292-3.
Meeting abstract

Reusch JEB, Rosenstock J, Bush MA, et al. Albiglutide, A long-acting GLP-1 receptor agonist, improves glycemia in type 2 diabetes: time-course analysis. Diabetes. 2009;58((Reusch J.E.B.; Rosenstock J.; Bush M.A.; Yang F.; Stewart M.W.)).
Meeting abstract

Rhoads GG, Dain MP, Zhang Q, et al. Two-year glycaemic control and healthcare expenditures following initiation of insulin glargine versus neutral protamine Hagedorn insulin in type 2 diabetes. Diabetes, Obesity and Metabolism. 2011;13(8):711-7.
No drug comparison of interest

Ridderstrale M, Svaerd R, Zeller C, et al. Rationale, design and baseline characteristics of a 4-year (208-week) phase III trial of empagliflozin, an SGLT2 inhibitor, versus glimepiride as add-on to metformin in patients with type 2 diabetes mellitus with insufficient glycemic control. Cardiovasc Diabetol. 2013;12(1).
No outcome of interest; No data from trial yet

Ridderstranullle M, Andersen KR, Zeller C, et al. Empagliflozin (EMPA) compared with glimepiride (GLIM) as addon to metformin (MET) for 2 years in patients with type 2 diabetes (T2DM). Diabetes. 2014;63((Ridderstranullle M.; Andersen K.R.; Zeller C.; Kim G.; Woerle H.J.; Broedl U.C.) Gentofte, Denmark, Asker, Norway, Biberach, Germany, Ingelheim, Germany):A70.
Meeting abstract

Ridderstranullle M, Andersen KR, Zeller C, et al. Empagliflozin compared with glimepiride as add-on to metformin for 2 years in patients with type 2 diabetes. Diabetologia. 2014;57(1):S7-S8.
Meeting abstract

Rijzewijk LJ, Van Der Meer RW, Lubberink M, et al. Differential action of pioglitazone and metformin on hepatic fat, substrate metabolism and perfusion in type 2 diabetic patients. Diabetologia. 2009;52(S1):S336.
Meeting abstract

Rizzo MR, Barbieri M, Boccardi V, et al. Dipeptidyl Peptidase-4 Inhibitors Have Protective Effect on Cognitive Impairment in Aged Diabetic Patients With Mild Cognitive Impairment. J Gerontol A Biol Sci Med Sci. 2014 Mar 26PMID: 24671867.
Does not account for confounding

Robin P, Bres V, Porokhov B, et al. Focus on medical history in incretin-based drugs inducing pancreatitis in patients with type 2 diabetes mellitus. Fundamental and Clinical Pharmacology. 2014;28((Robin P.; Bres V.; Hillaire-Buys D.; Petit P.; Faillie J.L.) Pharmacovigilance Regional Center, Department of Medical Pharmacology and Toxicology, CHRU Montpellier, Montpellier, France):51.
Meeting abstract

Roden M, Merker L, Christiansen AV, et al. Safety and tolerability of empagliflozin (EMPA) in phase III trials and their extensions in patients with type 2 diabetes (T2DM). Diabetologia. 2014;57(1):S325-S6.
Meeting abstract

Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy improves glucose control in drug-naive patients with type 2 diabetes (T2DM). Diabetes. 2013;62((Roden M.; Weng J.; Eilbracht J.; Delafont B.; Kim G.; Woerle H.J.; Broedl U.C.) Dusseldorf, Germany, Canton, China, Biberach, Germany, Reims, France, Ingelheim, Germany):A280.
Meeting abstract

Roden M, Weng J, Merker L, et al. Empagliflozin (EMPA) monotherapy for (greater-than or equal to)76 weeks in drug-naive patients with type 2 diabetes (T2DM). Diabetes. 2014;63((Roden M.; Weng J.; Merker L.; Christiansen A.V.; Roux F.; Salsali A.; Kim G.; Stella P.; Woerle H.J.; Broedl U.C.) Dusseldorf, Germany, Guangzhou, China, Dormagen, Germany, Copenhagen, Denmark, Reims, France, Ingelheim, Germany):A69.
Meeting abstract

Rodriguez A, Reviriego J, Karamanos V, et al. Management of cardiovascular risk factors with pioglitazone combination therapies in type 2 diabetes: an observational cohort study. Cardiovasc Diabetol. 2011;10:18. PMID: 21314919.
Does not account for confounding

Rohwedder K, Hruba V, Salsali A, et al. Dapagliflozin, a sodium-glucose cotransporter 2 inhibitor, has a low propensity to cause hypoglycemia in patients with type 2 diabetes. Diabetes. 2011;60((Rohwedder K.; Hruba V.; Salsali A.; Ying L.H.; Sugg J.; List J.F.; Parikh S.J.) Wedel, Germany):A286.
Meeting abstract

Rohwedder K, Johnsson E, Parikh S. Reduced risk of hypoglycaemic events with dapagliflozin vs glipizide as add-on therapy in type 2 diabetes mellitus: 4-year data from a phase 3 study. Diabetologia. 2014;57(1):S326.
Meeting abstract

Rohwedder K, Langkilde AM, Iqbal N, et al. Measures of (beta)-cell function and insulin sensitivity over time in patients with type 2 diabetes receiving dapagliflozin versus glipizide as add-on therapy to metformin. Endocr Rev. 2012;33(3).
Meeting abstract

Rohwedder K, Nauck MA, Duran-Garcia S, et al. Combined hba1c and weight reduction is achieved more frequently with add-on dapagliflozin than add-on glipizide in patients with type 2 diabetes inadequately controlled on metformin. Diabetes. 2013;62((Rohwedder K.; Nauck M.A.; Duran-Garcia S.; Hashemi M.; Parikh S.J.) Wedel, Germany, Bad Lauterberg, Germany, Sevilla, Spain, Molndal, Sweden, Wilmington, DE):A60-A1.
Meeting abstract

Rohwedder K, Nauck MA, Duran-Garcia S, et al. Combined HbA1c and weight reduction is more frequent with dapagliflozin vs glipizide add-on treatment in patients with type 2 diabetes inadequately controlled on metformin. Diabetologia. 2013;56((Rohwedder K.) AstraZeneca, Wedel, Germany):S376.
Meeting abstract

Rohwedder K, Parikh SJ, Johnsson E. Lower risk of hypoglycemic events with dapagliflozin than glipizide over 4 years in a

phase 3 study. Diabetes. 2014;63((Rohwedder K.; Parikh S.J.; Johnsson E.) Wedel, Germany, Wilmington, DE, Molndal, Sweden):A563-A4.
Meeting abstract

Rokeya B, Parvin M, Bhowmik A, et al. Randomized double-blind clinical trial comparaing efficacy and safety of pioglitazone and metformin in patients with type 2 diabetes. Diabetes. 2011;60((Rokeya B.; Parvin M.; Bhowmik A.; Chowdhury A.K.A.) Dhaka, Bangladesh):A618.
Meeting abstract

Rombopoulos G, Hatzikou M, Panitti E, et al. Association of hypoglycemia with different oral antidiabetic treatments and its impact on quality of life and disease control in patients with type 2 diabetes mellitus (the hypo study). Value in Health. 2014;17(7):A357.
Meeting abstract

Romero SP, Andrey JL, Garcia-Egido A, et al. Metformin therapy and prognosis of patients with heart failure and new-onset diabetes mellitus. A propensity-matched study in the community. International Journal of Cardiology. 2013;166(2):404-12.
Background medications

Romley JA, Goldman DP, Solomon M, et al. Exenatide therapy and the risk of pancreatitis and pancreatic cancer in a privately insured population. Diabetes Technol Ther. 2012 Oct;14(10):904-11. PMID: 22845701.
No drug comparison of interest

Romon I, Rey G, Mandereau-Bruno L, et al. The excess mortality related to cardiovascular diseases and cancer among adults pharmacologically treated for diabetes-the 2001-2006 ENTRED cohort. Diabetic Medicine. 2014;31(8):946-53.
Background medications; No drug comparison of interest

Rosenstock J, Fonseca VA, Gross JL, et al. Advancing Basal Insulin Replacement in Type 2 Diabetes Inadequately Controlled With Insulin Glargine Plus Oral Agents: A Comparison of Adding Albiglutide, a Weekly GLP-1 Receptor Agonist, Versus Thrice-Daily Prandial Insulin Lispro. Diabetes Care. 2014 Jun 4PMID: 24898300.
No drug comparison of interest

Rosenstock J, Gross JL, Salinas CAA, et al. Long-term safety and efficacy of saxagliptin after 4-year follow-up of patients with type 2 diabetes. Diabetes. 2011;60((Rosenstock J.; Gross J.L.; Salinas C.A.A.; Hissa M.; Berglind N.; Ravichandran S.; Fleming D.) Dallas, United States):A298.
Meeting abstract

Rosenstock J, Inzucchi S, Seufert J, et al. Efficacy and safety of alogliptin combined with pioglitazone in patients with type 2 diabetes inadequately controlled with diet and exercise. Diabetes. 2009;58((Rosenstock J.; Inzucchi S.; Seufert J.; Fleck P.; Wilson C.; Mekki Q.)).
Meeting abstract

Rosenstock J, Inzucchi SE, Seufert J, et al. Combination alogliptin plus pioglitazone treatment in patients with type 2 diabetes inadequately controlled with diet and exercise. Canadian Journal of Diabetes. 2009;33(3):212.
Meeting abstract

Rosenstock J, Jelaska A, Kim G, et al. Empagliflozin as add-on to basal insulin for 78 weeks improves glycaemic control with weight loss in patients with Type 2 diabetes: A phase III, randomised, double-blind trial (EMPA-REG BASAL(trademark)). Diabetic Medicine. 2014;31((Rosenstock J.) Dallas

Diabetes and Endocrine Center at Medical City, Dallas, United States):64.
Meeting abstract

Rosenstock J, Jelaska A, Seman L, et al. Efficacy and safety of BI 10773, a new sodium glucose cotransporter-2 (SGLT-2) inhibitor, in type 2 diabetes inadequately controlled on metformin. Diabetes. 2011;60((Rosenstock J.; Jelaska A.; Seman L.; Pinnetti S.; Hantel S.; Woerle H.J.) Dallas, United States):A271.
Meeting abstract

Rosenstock J, Polidori D, Zhao Y, et al. Canagliflozin, an inhibitor of sodium glucose co-transporter 2, improves glycaemic control, lowers body weight, and improves beta cell function in subjects with type 2 diabetes on background metformin. Diabetologia. 2010;53((Rosenstock J.) Dallas Diabetes and Endocrine Center, Dallas, United States):S349.
Meeting abstract

Rosenstock J, Rendell MS, Gross JL, et al. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycaemia. Diabetes Obes Metab. 2009 Dec;11(12):1145-52. PMID: 19758359.
No drug comparison of interest

Rosenstock J, Reusch J, Bush M, et al. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. Diabetes Care. 2009 Oct;32(10):1880-6. PMID: 19592625.
Background medications

Rosenstock J, Reusch J, Bush M, et al. Weekly, biweekly, and monthly albiglutide improves measures of glycaemia in patients with type 2 diabetes on background metformin therapy. Canadian Journal of Diabetes. 2009;33(3):211.
Meeting abstract

Rosenstock J, Reusch JEB, Bush MA, et al. The potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: A randomized controlled trial exploring weekly, biweekly and monthly dosing. Diabetes. 2009;58((Rosenstock J.; Reusch J.E.B.; Bush M.A.; Yang F.; Stewart M.W.)).
Meeting abstract

Rosenstock J, Reusch JEB, Bush MA, et al. Weekly, biweekly and monthly efficacy of albiglutide, a long-acting GLP-1-receptor agonist, in patients with type 2 diabetes receiving concomitant background metformin. Diabetologia. 2009;52(S1):S288.
Meeting abstract

Rosenstock J, Rosenberg N, Riddle MC, et al. The impact of age and disease duration on glycemic control and lipid profile: Insulin glargine vs thiazolidinediones in type 2 diabetes. Diabetes. 2009;58((Rosenstock J.; Rosenberg N.; Riddle M.C.; Meneghini L.F.; Chaudhuri A.)).
Meeting abstract

Rosenstock J, Vico M, Wei L, et al. Dapagliflozin added-on to pioglitazone reduces HbA1c and mitigates weight gain with low incidence of hypoglycemia in type 2 diabetes. Diabetes. 2011;60((Rosenstock J.; Vico M.; Wei L.; Salsali A.; List J.) Dallas, United States):A270.
Meeting abstract

Rosenstock J, Vico M, Wei L, et al. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone

monotherapy. Diabetes Care; 2012. p. 1473-8.
No drug comparison of interest; Background medications

Rosenstock J, Wei W, Davis KL, et al. Effects of exenatide, sitagliptin, and insulin on weight and glycemic control in a real-world setting. Diabetes. 2009;58((Rosenstock J.; Wei W.; Davis K.L.; Berria R.)).
Meeting abstract

Ross S, Thamer C, Cescutti J, et al. Empagliflozin twice daily versus once daily as add-on to metformin in patients with type 2 diabetes. Diabetologia. 2014;57(1):S345.
Meeting abstract

Ross SA, Caballero AE, Del Prato S, et al. Initial combination of linagliptin and metformin compared with linagliptin monotherapy in patients with newly diagnosed type 2 diabetes and marked hyperglycaemia: a randomized, double-blind, active-controlled, parallel group, multinational clinical trial. Diabetes Obes Metab. 2015 Feb;17(2):136-44. PMID: 25298165.
No drug comparison of interest

Ross SA, Haak T, Patel S, et al. Safety and tolerability of linagliptin and metformin in combination for patients with type 2 diabetes mellitus (T2DM). Diabetes. 2014;63((Ross S.A.; Haak T.; Patel S.; Thiemann S.; Schumacher H.; Meinicke T.) Calgary, AB, Canada, Bad Mergentheim, Germany, Bracknell, United Kingdom, Ingelheim, Germany, Biberach, Germany):A277.
Meeting abstract

Roumie CL, Huizinga MM, Liu X, et al. The effect of incident antidiabetic regimens on lipid profiles in veterans with type 2 diabetes: a retrospective cohort. Pharmacoepidemiol Drug Saf. 2011 Jan;20(1):36-44. PMID: 21182152.
No outcome of interest

Round EM, Engel SS, Golm GT, et al. Safety of sitagliptin in elderly patients with type 2 diabetes: a pooled analysis of 25 clinical studies. Drugs Aging. 2014 Mar;31(3):203-14. PMID: 24510656.
Background medications

Roussel R, De Zeeuw D, Law G, et al. Efficacy and safety of canagliflozin (CANA) in patients with type 2 diabetes mellitus (T2DM) who progressed to stage 3A chronic kidney disease during treatment. Diabetologia. 2014;57(1):S322-S3.
Meeting abstract

Roussel R, Hadjadj S, Pasquet B, et al. Thiazolidinedione use is not associated with worse cardiovascular outcomes: a study in 28,332 high risk patients with diabetes in routine clinical practice: brief title: thiazolidinedione use and mortality. Int J Cardiol. 2013 Aug 20;167(4):1380-4. PMID: 22560911
No drug comparison of interest

Roussel R, Travert F, Pasquet B, et al. Metformin use and mortality among patients with diabetes and atherothrombosis. Arch Intern Med. 2010 Nov 22;170(21):1892-9. PMID: 21098347.
Background medications

Rubin M, Manavalan J, Agarwal S, et al. Effects of Rosiglitazone vs Metformin on Circulating Osteoclast and Osteogenic Precursor Cells in Postmenopausal Women with Type 2 Diabetes Mellitus. J Clin Endocrinol Metab. 2014 Jun 6:jc20133666. PMID: 24905061.
No outcome of interest

Ruiter R, Visser LE, van Herk-Sukel MP, et al. Lower risk of cancer in patients on metformin in comparison with those on sulfonylurea derivatives: results from a large population-based follow-up study. Diabetes Care. 2012 Jan;35(1):119-24. PMID: 22100960.
Does not account for confounding; Background medications

Saab C, Al-Saber FA, Haddad J, et al. Effectiveness and tolerability of second-line treatment with vildagliptin versus other oral drugs for type 2 diabetes in a real-world setting in the middle east: Results from the edge study. Vascular Health and Risk Management. 2015;11((Saab C.) Department of endocrinology and Metabolism, Sacre Coeur University Hospital, Baabda, Lebanon):149-55.
No drug comparison of interest

Saadatnia M, Siavash M, Amini A, et al. Cognitive impairment in type 2 diabetic patients using metformin or sulfonylurea: A comparative study. Alzheimer's and Dementia. 2009;5(4):390.
Meeting abstract

Sabale U, Ekman M, Granstrom O, et al. Cost-effectiveness of dapagliflozin (Forxiga) added to metformin compared with sulfonylurea added to metformin in type 2 diabetes in the Nordic countries. Prim Care Diabetes. 2014 May 16PMID: 24840612.
No original data; Does not meet study design criteria

Saglietti G, Placentino G, Schellino A. Observational Study on Dipeptidyl Peptidase-4 Inhibitors: A Real-Life Analysis on 360 Patients from the ASL VCO Territory in Italy. Clin Drug Investig. 2014 Jul;34(7):513-9. PMID: 24788571.
Background medications

Sahin IH, Hassabo HM, Shen Y, et al. Validation of the survival benefit from metformin use in patients with type 2 diabetes and colorectal cancer. Journal of Clinical Oncology. 2013;31(4).
Meeting abstract

Saiki A, Ohira M, Endo K, et al. Pioglitazone decreases plasma angiotensin II concentration in type 2 diabetes. J Atheroscler Thromb. 2010 Jun 30;17(6):651-7. PMID: 20467188.
Background medications; No drug comparison of interest

Sakai Y, Suzuki A, Mugishima K, et al. Effects of alogliptin in chronic kidney disease patients with type 2 diabetes. Intern Med. 2014;53(3):195-203. PMID: 24492687.
No drug comparison of interest; Does not meet study design criteria

Sakoda LC, Achacoso NS, Quesenberry CP, et al. Metformin use and risk of lung cancer in patients with diabetes. Cancer Research. 2013;73(8).
Meeting abstract

Salerno Soares RL, Cruz Filho RA, Parada B, et al. Correlation between gastrointestinal symptoms(GI) with clinical factors and the treatment with Metformin in Diabetis Type 2 (type2DM) patients. Neurogastroenterology and Motility. 2012;24((Salerno Soares R.L.; Cruz Filho R.A.; Parada B.; Bromonschenkel Brandao I.; Queiroz Micuci A.; Dias Goncalves C.) Federal Fluminense University, Dept. of Internal Medicine, Niteroi, Brazil):186-7.
Meeting abstract

Salsali A, Hruba V, Ying L, et al. Reduction in postprandial glucose with dapagliflozin in type 2 diabetes. Diabetes. 2011;60((Salsali

A.; Hruba V.; Ying L.; Wei L.; Sugg J.E.; List J.F.; Parikh S.) Princeton, United States):A303.
Meeting abstract

Salsali A, Tang W, List JF, et al. Efficacy of dapagliflozin as monotherapy administered in the morning or evening to treat type 2 diabetes mellitus. Diabetologia. 2010;53((Salsali A.; Tang W.; List J.F.) Bristol Myers Squibb, Princeton, United States):S346.
Meeting abstract

Salvadeo SAT, Maffio P, Ferrari I, et al. Comparison between exenatide and glimepiride on metabolic control and on insulin resistance in type 2 diabetic patients with metformin therapy. Diabetologia. 2010;53((Salvadeo S.A.T.; Maffio P.; Ferrari I.; D'Angelo A.; Dero G.) Internal Medicine and Therapeutics, University of Pavia, IRCCS Policlinico S.Matteo, Bergamo, Italy):S339-S40.
Meeting abstract

Sanaiha Y, Thompson C, Elashoff D, et al. Metformin use and recurrence in patients with oral cavity/oropharynx squamous cell carcinoma. Journal of Investigative Medicine. 2013;61(1):133.
Meeting abstract

Saravanan K, Manna PK, Mohanta GP. A study on assessment and comparison of anti diabetic effect of monotherapy and combination therapy involving in Metformine and Glimipride. Journal of Pharmaceutical Sciences and Research. 2014;6(1):11-4.
Does not meet study design criteria

Sasaki S, Sako Y, Hirata E, et al. In Japanese patients with type 2 diabetes, clinical predictors for effectiveness of liraglutide treatment are different between obese and non-obese patients. Diabetes. 2012;61((Sasaki S.; Sako Y.; Hirata E.; Sakai Y.; Inoguchi T.; Takayanagi R.) Fukuoka City, Japan):A612.
Meeting abstract

Satoh-Asahara N, Sasaki Y, Wada H, et al. A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism. 2013 Mar;62(3):347-51. PMID: 23062489.
Background medications; Placebo-controlled trial

Saunders W, Nguyen H, Kalsekar I. Real-world comparative effectiveness of exenatide once weekly and liraglutide in patients with type 2 diabetes mellitus. Diabetes. 2014;63((Saunders W.; Nguyen H.; Kalsekar I.) Charlotte, NC, Plainsboro, NJ):A310.
Meeting abstract

Sayo Y, Ishiko T. Clinical efficacy of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes for 6 months. Therapeutic Research. 2011;32(4):523-9.
No drug comparison of interest

Scheel-Thomsen J, Starup-Linde J, Gejl M, et al. Diabetes and stroke: Liraglutide is associated with a decreased risk of stroke in type 2 diabetes mellitus. A nested case-control study. Journal of Neurology. 2014;261((Scheel-Thomsen J.) Department of Neurology, Aalborg University Hospital, Aalborg, Denmark):S109.
Meeting abstract

Scheen AJ, Tan MH, Betteridge DJ, et al. Long-term glycaemic effects of pioglitazone compared with placebo as add-on treatment to metformin or sulphonylurea monotherapy in PROactive (PROactive 18). Diabet Med. 2009 Dec;26(12):1242-9. PMID: 20002476.

Does not account for confounding; Background medications

Scheen AJ, Van Gaal LF. [Glycemic control before and after sitagliptin in general medical practice: analysis of determinant factors in the Belgian observational study "SUGAR"]. Rev Med Liege. 2011 Jul-Aug;66(7-8):440-6. PMID: 21942079.
No long-term outcomes or adverse events; No drug comparison of interest

Scheen AJ, Van Gaal LF. [Sugar: results of a Belgian observational study on the use of sitagliptin in patients with type 2 diabetes]. Rev Med Liege. 2010 Mar;65(3):127-32. PMID: 20411816.
No outcome of interest

Schernthaner G, Forst T, Gulba D, et al. Challenge in diabetes therapy: Effects of thiazolidinediones beyond blood glucose control. Deutsche Medizinische Wochenschrift. 2009;134(18):949-54.
No original data

Schernthaner G, Gross JL, Rosenstock J, et al. Erratum: Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: A 52-week randomized trial (Diabetes Care (2013) 36 (2508-2515)). Diabetes Care. 2013;36(12):4172.
No original data

Schernthaner G, Khunti K, Patel S, et al. Safety of linagliptin in 8,778 patients with type 2 diabetes mellitus: Pooled analysis of 23 placebo-controlled, randomized clinical trials. Diabetes. 2014;63((Schernthaner G.; Khunti K.; Patel S.; Cheng K.; Mattheus M.; Woerle H.-J.) Vienna, Austria, Leicester, United Kingdom, Bracknell, United Kingdom, Ingelheim, Germany):A281.
Meeting abstract

Schernthaner G, Khunti K, Patel S, et al. Safety of linagliptin in 8778 patients with type 2 diabetes mellitus: Pooled analysis of 23 placebo-controlled randomised clinical trials. Diabetologia. 2014;57(1):S360.
Meeting abstract

Schernthaner G, Von Eynatten M, Emser A, et al. Safety and tolerability of linagliptin: A pooled analysis of data from 3572 patients with type 2 diabetes. Diabetes. 2011;60((Schernthaner G.; Von Eynatten M.; Emser A.; Patel S.; Woerle H.J.) Vienna, Austria):A619.
Meeting abstract

Schloot N, Haupt A, Schutt M, et al. Severe hypoglycemia during therapy with sulfonylurea in patients with type 2 diabetes (T2D) in Germany/Austria: Event rate and identification of patients at risk. Diabetologia. 2014;57(1):S265.
Meeting abstract

Schlosser A, Owens D, Taskinen MR, et al. Long-term safety and efficacy of the DPP-4 inhibitor linagliptin: Data from a large 2-year study in subjects with type 2 diabetes mellitus. Diabetologia. 2011;54((Schlosser A.) Boehringer Ingelheim, Alkmaar, Netherlands):S108.
Meeting abstract

Schmidt WE, Christiansen JS, Hammer M, et al. Patient reported outcomes are superior in patients with type 2 diabetes (T2D treated with Liraglutide as compared to exenatide, when added to metformin, sulfonylurea or both. Diabetes. 2009;58((Schmidt W.E.; Christiansen J.S.; Hammer M.; Zychma M.; Buse J.)).
No outcome of interest; No drug comparison of interest

Schmidt WE, Christiansen JS, Hammer M, et al. Patient reported outcomes are superior in patients with type 2 diabetes treated with liraglutide as compared to exenatide,when added to metformin,sulfonylurea or both. Value in Health. 2009;12(3):A105.
Meeting abstract

Schmidt WE, Christiansen JS, Hammer M, et al. Patient-reported outcomes are superior in patients with Type 2 diabetes treated with liraglutide as compared with exenatide, when added to metformin, sulphonylurea or both: results from a randomized, open-label study. Diabet Med. 2011 Jun;28(6):715-23. PMID: 21388442.
Background medications; No outcome of interest

Schnell O. [Oral add-on therapy to metformin in type 2 diabetes mellitus: a direct comparison between canagliflozin and sitagliptin]. Dtsch Med Wochenschr. 2014 Feb;139 Suppl 2:S70-4. PMID: 24481636.
Non-English language

Schoenauer M, Karagiannis E, Lundershausen R, et al. Weight effects of combination treatment with insulin and pioglitazone. Diabetes. 2009;58((Schoenauer M.; Karagiannis E.; Lundershausen R.; Grueneberg M.; Kroeger J.; Heddaeus H.)).
Meeting abstract

Schramm TK, Gislason GH, Rasmussen JN, et al. Differences in risk of all-cause death according to metformin in different dual combinations in patients with diabetes: A nationwide study. European Heart Journal. 2010;31((Schramm T.K.; Kober L.) Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark):517.
Meeting abstract

Schutt M, Kern W, Zimmermann A, et al. Association of antidiabetic therapies to glycemic control and to body weight in type 2 diabetes: a German multicenter analysis on 9294 patients. Exp Clin Endocrinol Diabetes. 2010 Aug;118(8):490-5. PMID: 20200811.
Does not meet study design criteria; No drug comparison of interest

Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26. PMID: 23992601.
Background medications

Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26. PMID: 23992601.
Does not account for confounding; Does not meet study design criteria

Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation. 2014 Oct 28;130(18):1579-88. PMID: 25189213.
Background medications; No drug comparison of interest

Scirica BM, Raz I, Cavender MA, et al. Outcomes of patients with type 2 diabetes and known congestive heart failure treated with saxagliptin: Analyses of the savor-TIMI 53 study. Circulation. 2013;128(22).
Meeting abstract

Scorsone A, Ferrara L, Spano L, et al. Influence of exenatide therapy on diabetes management in type 2 diabetes subjects ketosis prone at the onset. Italian Journal of Medicine. 2013;7((Scorsone A.; Ferrara L.;

Spano L.; Di Noto A.; Aiello V.; Saura G.; Fleres M.) UO Diabetologia, Italy):111.
Scott D. Treatment of type 2 diabetes in chronic kidney disease: a case for linagliptin in the treatment of diabetes in severe renal impairment. Diabetes Metab Syndr Obes. 2013;6:359-63. PMID: 24124385.
Meeting abstract

Scott LJ. Linagliptin: in type 2 diabetes mellitus. Drugs. 2011 Mar 26;71(5):611-24. PMID: 21443284.
No original data

Seck T, Engel SS, Chen Y, et al. Sitagliptin (SITA) provides similar glycemic control with weight loss and less hypoglycemia compared to sulfonylurea (SU) in older patients with type 2 diabetes (T2DM). Diabetes. 2011;60((Seck T.; Engel S.S.; Chen Y.; Golm G.T.; Davies M.J.; Kaufman K.D.; Goldstein B.) Whitehouse Station, United States):A620-A1.
Meeting abstract

Seck T, Williams-Herman DE, Chen Y, et al. Sitagliptin compared with the sulfonylurea glimepiride provides similar efficacy with less hypoglycemia and no weight gain when added to ongoing metformin therapy in patients with type 2 diabetes mellitus (T2DM). Diabetologie und Stoffwechsel. 2010;5((Seck T.; Williams-Herman D.E.; Chen Y.; Duran L.; Johnson-Levonas A.O.; Kaufman K.D.; Goldstein B.J.) Merck Sharp and Dohme, Rahway, United States).
Meeting abstract

Seck TL, Engel SS, Williams-Herman DE, et al. Sitagliptin more effectively achieves a composite endpoint for A1C reduction, lack of hypoglycemia and no body weight gain compared with glipizide. Diabetes Res Clin Pract. 2011 Jul;93(1):e15-7. PMID: 21477878.
No outcome of interest

Seino Y, Fujita T, Hiroi S, et al. Efficacy and safety of alogliptin in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, dose-ranging comparison with placebo, followed by a long-term extension study. Curr Med Res Opin. 2011 Sep;27(9):1781-92. PMID: 21806314.
No drug comparison of interest; Placebo-controlled trial

Seino Y, Inagaki N, Miyahara H, et al. A randomized dose-finding study demonstrating the efficacy and tolerability of albiglutide in Japanese patients with type 2 diabetes mellitus. Curr Med Res Opin. 2014 Jun;30(6):1095-106. PMID: 24552155.
Placebo-controlled trial; Background medications

Seino Y, Inagaki N, Miyahara H, et al. Albiglutide significantly lowers glycemia in japanese patients with type 2 diabetes (T2D). Diabetes. 2012;61((Seino Y.; Inagaki N.; Miyahara H.; Okuda I.; Bush M.; Yang F.; Ye J.; Holland C.; Johnson S.; Lewis E.; Nakajima H.) Osaka, Japan):A248.
Meeting abstract

Seino Y, Nakajima H, Miyahara H, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of albiglutide, a long-acting GLP-1-receptor agonist, in Japanese subjects with type 2 diabetes mellitus. Curr Med Res Opin. 2009 Dec;25(12):3049-57. PMID: 19863477.
Placebo-controlled trial

Seino Y, Rasmussen MF, Clauson P, et al. The once-daily human glucagon-like peptide-1 analog, liraglutide, improves beta-cell function in Japanese patients with type 2 diabetes. J Diabetes Investig. 2012 Aug 20;3(4):388-95. PMID: 24843595.
No drug comparison of interest

Seino Y, Rasmussen MF, Nishida T, et al. Glucagon-like peptide-1 analog liraglutide in combination with sulfonylurea safely improves blood glucose measures vs sulfonylurea monotherapy in Japanese patients with type 2 diabetes: Results of a 52-week, randomized, multicenter trial. J Diabetes Investig. 2011 Aug 2;2(4):280-6. PMID: 24843499.
No drug comparison of interest

Seman L, Rosenstock J, Jelaska A, et al. ENCORE: Efficacy and safety of BI 10773, a new sodium glucose cotransporter- 2 (SGLT-2) inhibitor, in type 2 diabetes patients inadequately controlled on metformin. Diabetologia. 2011;54((Seman L.; Jelaska A.) Boehringer Ingelheim Pharma Inc., Ridgefield, United States):S67-S8.
Meeting abstract

Seong J, Choi N, Kim J, et al. Dipeptidyl peptidase-4 inhibitor use and risk of acute pancreatitis in patients with type 2 diabetes. Drug Safety. 2013;36(9):856.
Meeting abstract

Seong JM, Choi NK, Jung SY, et al. A comparison of pioglitazone vs rosiglitazone for heart failure in elderly type 2 patients. Pharmacoepidemiology and Drug Safety (PDS). 2009;18(S1):S153.
Meeting abstract

Seong JM, Choi NK, Shin JY, et al. Comparative effectiveness of dipeptidyl peptidase-4 inhibitor for the risk of cardiovascular and cerebrovascular disease in patients with type 2 diabetes. Pharmacoepidemiology and Drug Safety. 2012;21((Seong J.-M.; Shin J.-Y.; Kim Y.-J.; Park B.-J.) Department of Preventive Medicine, Seoul National University, College of Medicine, Seoul, South Korea):237.
Meeting abstract

Sethi B, Comlekci A, Gomez-Peralta F, et al. Relationship between glycaemic control and hypoglycaemia using insulin glargine versus premixed insulin in type 2 diabetes: A subanalysis of GALAPAGOS. Diabetologia. 2013;56((Sethi B.) CARE Hospital, Hyderabad, India):S240.
Meeting abstract

Seufert J, Bailey TS, Svendsen CB, et al. The effect of liraglutide on A1c and body weight is largely dependent on diabetes duration. Diabetes. 2013;62((Seufert J.; Bailey T.S.; Svendsen C.B.; Donsmark M.; Nauck M.A.) Freiburg, Germany, Escondido, CA, Soborg, Denmark, Bad Lauterberg, Germany):A266.
Meeting abstract

Seufert J. [Oral add-on therapy to metformin in type 2 diabetes mellitus: a direct comparison beween canagliflozin and glimepiride]. Dtsch Med Wochenschr. 2014 Feb;139 Suppl 2:S65-9. PMID: 24481635.
No original data

Sha S, Polidori D, Heise T, et al. Effect of the Sodium Glucose Co-transporter 2 Inhibitor, Canagliflozin, on Plasma Volume in Patients With Type 2 Diabetes Mellitus. Diabetes Obes Metab. 2014 Jun 17PMID: 24939043.
Background medications

Shah DD, Fonarow GC, Horwich TB. Metformin therapy and outcomes in patients with advanced systolic heart failure and diabetes. J Card Fail. 2010 Mar;16(3):200-6. PMID: 20206893.
Background medications

Shah N, Amanullah, Afridi MH, et al. Prevelance, risk factors and outcomes of hypoglycemia in elderly diabetic patients. JPMI - Journal of Postgraduate Medical Institute. 2012;26(3):272-6.
Background medications; Does not meet study design criteria

Shani M, Feldman L, Kaiserman I, et al. Is rosiglitazone use associated with an increase in intensive eye treatment in diabetic patients? A community based study. Eur J Gen Pract. 2011 Dec;17(4):205-9. PMID: 21745121.
No drug comparison of interest; Background medications

Shankar R, Engel SS, Xu L, et al. Sitagliptin provides similar glycaemic improvement with less hypoglycaemia in the elderly with type 2 diabetes mellitus compared to sulphonylurea. Diabetologia. 2012;55((Shankar R.; Engel S.S.; Xu L.; Golm G.T.; Davies M.J.; Kaufman K.D.; Goldstein B.J.) Merck Sharp and Dohme, Whitehouse Station, United States):S344-S5.
Meeting abstract

Shankar R, Engel SS, Xu L, et al. Sitagliptin provides similar glycemic improvement with less hypoglycemia in the elderly with type 2 diabetes mellitus compared to sulfonylurea. Diabetes. 2012;61((Shankar R.; Engel S.S.; Xu L.; Golm G.T.; Davies M.J.; Kaufman K.D.; Goldstein B.J.) Whitehouse Station, United States):A278.
Meeting abstract

Shankar RR, Xu L, Golm GT, et al. A comparison of glycaemic effects of sitagliptin and sulfonylureas in elderly patients with type 2 diabetes mellitus. Int J Clin Pract. 2015 Feb 4PMID: 25652751.
Background medications

Shaqdan W, Abdulwahid NA. Addition of pioglitazone to type 2 diabetic patients with uncontrolled diabetes regardless of their medication status. Diabetes. 2009;58((Shaqdan W.; Abdulwahid N.A.)).
Meeting abstract

Shaya FT, Lu Z, Sohn K, et al. Thiazolidinediones and cardiovascular events in high-risk patients with type-2 diabetes mellitus: a comparison with other oral antidiabetic agents. P T. 2009 Sep;34(9):490-501. PMID: 20140111.
Background medications; No drug comparison of interest

Sheehan J, Moorthy V, Colilla S, et al. Charges and health care resource use in patients with type 2 diabetes melitus after treatment initiation with saxagliptin or sitagliptin. Value in Health. 2014;17(3):A245.
Meeting abstract

Shi L, Zhao Y, Szymanski K, et al. Impact of thiazolidinedione safety warnings on medication use patterns and glycemic control among veterans with diabetes mellitus. J Diabetes Complications. 2011 May-Jun;25(3):143-50. PMID: 20708416.
No drug comparison of interest; No outcome of interest

Shimoda S, Iwashita S, Sekigami T, et al. Comparison of the efficacy of sitagliptin and glimepiride dose-up in Japanese patients with type 2 diabetes poorly controlled by sitagliptin and glimepiride in combination. J Diabetes Investig. 2014 May 4;5(3):320-6. PMID: 24843781.
No drug comparison of interest

Shin MS, Yu JH, Jung CH, et al. The duration of sulfonylurea treatment is associated with beta-cell dysfunction in patients with type 2 diabetes mellitus.

Diabetes Technol Ther. 2012 Nov;14(11):1033-42. PMID: 22958196.
No drug comparison of interest; No outcome of interest

Sicras Mainar A, Roldan Suarez C, Font Ramos B, et al. Clinical and economical consequences of the combination of metformin with dipeptidyl peptidase inhibitors in type 2 diabetes patients. Rev Clin Esp. 2013 Nov;213(8):377-84. PMID: 23870706.
Does not account for confounding; No drug comparison of interest

Sicras-Mainar A, Navarro-Artieda R. [Combination therapy of metformin vs dipeptidulpeptidase inhibitors and sulfonylureas in type 2 diabetes: clinical and economic impact]. Rev Peru Med Exp Salud Publica. 2014 Dec;31(4):626-34. PMID: 25597711.
Non-English language

Sicras-Mainar A, Navarro-Artieda R. Metformin in combination with dipeptidyl peptidase-4 inhibitors or sulfonylureas in the treatment of type 2 diabetes: Clinical and economic impact. Value in Health. 2014;17(7):A339-A40.
Meeting abstract

Sicras-Mainar A, Navarro-Artieda R. Use of metformin and vildagliptin for treatment of type 2 diabetes in the elderly. Drug Des Devel Ther. 2014;8:811-8. PMID: 24970999.
No drug comparison of interest

Siddiqi AI, Nambi S. Head to head comparison of glucagon-like peptide 1 (GLP-1) agonists and insulin in patients with Type 2 diabetes. Diabetic Medicine. 2013;30((Siddiqi A.I.; Nambi S.) Diabetes and Endocrinology, Colchester General Hospital, Colchester, United Kingdom):163.

Sideleva O, Tharp WG, Ferro AJ, et al. Pioglitazone increases glucose dependent insulinotropic receptor (GIPR) expression in adipocytes in patients with type 2 diabetes. Diabetes. 2011;60((Sideleva O.; Tharp W.G.; Ferro A.J.; Maple R.P.; Pratley R.E.) Colchester, United States):A437.
Meeting abstract

Signorovitch J, Macaulay D, Diener M, et al. Hypoglycaemia and accident risk in people with Type 2 diabetes treated with antidiabetes drugs without insulin. Diabetic Medicine. 2012;29((Signorovitch J.; Wu E.Q.) Health Care Practice, Analysis Group Inc., Boston, United States):21.
Meeting abstract

Simeone JC, Quilliam BJ. Predictors of emergency department and outpatient visits for hypoglycemia in type 2 diabetes: an analysis of a large US administrative claims database. Ann Pharmacother. 2012 Feb;46(2):157-68. PMID: 22234990.
Does not meet study design criteria; Background medications

Simeone JC, Quilliam BJ. Predictors of outpatient visits for hypoglycemia in type 2 diabetes patients on oral antidiabetic agents. Diabetes. 2011;60((Simeone J.C.; Quilliam B.J.) Kingston, United States):A137.
Meeting abstract

Simo R, Guerci B, Schernthaner G, et al. Long-term administration of exenatide and changes in body weight and markers of cardiovascular risk: A comparative study with glimepiride. Diabetologia. 2012;55((Simo R.) Vall d'Hebron Research Institute, Barcelona, Spain):S322.
Meeting abstract

Simo R, Plana-Ripoll O, Puente D, et al. Impact of glucose-lowering agents on the risk of cancer in type 2 diabetic patients.

The barcelona case-control study. PLoS One. 2013;8(11):e79968. PMID: 24278227.
No drug comparison of interest

Simon ACR, G.W TJ, Valkhoff VE, et al. Use of glucose lowering drugs and the risk of adenocarcinoma among patients with type 2 diabetes: A case-control study in the Netherlands. Diabetologia. 2013;56((Simon A.C.R.; Hoekstra J.B.L.; Holleman F.) Internal Medicine, Academical Medical Center, Amsterdam, Netherlands):S320.
Meeting abstract

Simon D, Bradley C, Gonder-Frederick L, et al. The panorama pan-European survey: Hypoglycaemia associated with different pharmacological treatments for type 2 diabetes. Value in Health. 2010;13(7):A297.
Meeting abstract

Sin HY, Kim JY, Jung KH. Total cholesterol, high density lipoprotein and triglyceride for cardiovascular disease in elderly patients treated with metformin. Arch Pharm Res. 2011 Jan;34(1):99-107. PMID: 21468921.
No drug comparison of interest; Placebo-controlled trial

Sinagra E, Mocciaro F, Messina M, et al. Colorectal cancer in patients with type 2 diabetes mellitus: Preliminary results froma retrospective analysis of 741 cases. Digestive and Liver Disease. 2013;45((Sinagra E.; Perricone G.; Orlando E.; Orlando A.; Scalisi A.; Cottone M.) Ospedali riuniti Villa Sofia-Cervello, Palermo, Italy):S173.
Meeting abstract

Sinagra E, Raimondo D, Messina M, et al. Colorectal cancer in patients with type 2 diabetes mellitus: Preliminary results from an ongoing case-control study. Digestive and Liver Disease. 2014;46((Sinagra E.; Raimondo D.; Messina M.) Fondazione Istituto San Raffaele - G. Giglio, Cefalu, Italy):S102.
Meeting abstract

Sinclair A, Bode B, Harris S, et al. Efficacy and safety of canagliflozin in older subjects with type 2 diabetes mellitus. Diabetologia. 2013;56((Sinclair A.) Luton and Dunstable University Hospital, Luton, United Kingdom):S383.
Meeting abstract

Singh S, Chang HY, Richards TM, et al. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. JAMA Intern Med. 2013 Apr 8;173(7):534-9. PMID: 23440284.
No drug comparison of interest; Does not meet study design criteria

Singh S, Chang HY, Richards TM, et al. Glucagon-like peptide-1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes: Population based matched case-control study. Journal of General Internal Medicine. 2013;28((Singh S.; Chang H.-Y.; Richards T.M.; Weiner J.; Clark J.M.; Segal J.B.) Johns Hopkins University, Baltimore, United States):S82.
Meeting abstract

Singh S, Chang HY, Richards TM, et al. Glucagon-like peptide-1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes: Population based matched case-control study. Pharmacoepidemiology and Drug Safety. 2013;22((Singh S.; Clark J.M.; Segal J.B.) Medicine, Johns Hopkins University, Baltimore, United States):26-7.
Meeting abstract

Singh S, Chang HY, Richards TM, et al. Thiazolidinedione use and risk of hospitalization for pneumonia in type 2 diabetes: Population based matched case-control study. Pharmacoepidemiology and Drug Safety. 2013;22((Singh S.; Clark J.; Segal J.B.) Medicine, Johns Hopkins University, Baltimore, United States):122.
Meeting abstract

Singh-Franco D, McLaughlin-Middlekauff J, Elrod S, et al. The effect of linagliptin on glycaemic control and tolerability in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab. 2012 Aug;14(8):694-708. PMID: 22340363.
Handsearch

Sjostrom CD, Hashemi M, Sugg J, et al. Dapagliflozin-induced weight loss impacts 24 week HbA1c and blood pressure levels. Diabetologia. 2013;56((Sjostrom C.D.; Hashemi M.; Johnsson E.) AstraZeneca, Molndal, Sweden):S81.
Meeting abstract

Sjostrom CD, Sugg J, Tjoen C, et al. Pilot analysis of the effect of the SGLT2 inhibitor dapagliflozin on blood pressure in patients with type 2 diabetes mellitus: A pooled analysis of placebo controlled trials. European Heart Journal. 2012;33((Sjostrom C.D.) AstraZeneca, Molndal, Sweden):680.
Meeting abstract

Sjostrom D, Johansson P, Ptaszynska A, et al. Dapagliflozin lowers blood pressure in hypertensive and nonhypertensive patients with type 2 diabetes. Diabetologia. 2014;57(1):S332-S3.
Meeting abstract

Sjostrom D, Ptaszynska A, List JF, et al. Dapagliflozin lowers blood pressure in patients with type 2 diabetes. Diabetes. 2014;63((Sjostrom D.; Ptaszynska A.; List J.F.; Johnsson E.) Moln - dal, Sweden, Princeton, NJ):A613.
Meeting abstract

Skrivanek Z, Chien JY, Gaydos B, et al. Dose-finding results in an adaptive trial of dulaglutide combined with metformin in type 2 diabetes (AWARD-5). Diabetes. 2013;62((Skrivanek Z.; Chien J.Y.; Gaydos B.; Heathman M.; Geiger M.J.; Milicevic Z.) Indianapolis, IN, Santa Clara, CA, Vienna, Austria):A269.
Meeting abstract

Sloan L, Newman J, Sauce C, et al. Safety and efficacy of linagliptin in type 2 diabetes patients with severe renal impairment. Diabetes. 2011;60((Sloan L.; Newman J.; Sauce C.; Von Eynatten M.; Patel S.; Woerle H.J.) Lufkin, United States):A114.
Meeting abstract

Smiechowski B, Azoulay L, Yin H, et al. The use of metformin and colorectal cancer incidence in patients with type II diabetes mellitus. Cancer Epidemiol Biomarkers Prev. 2013 Oct;22(10):1877-83. PMID: 23966577.
No drug comparison of interest

Smiechowski BB, Azoulay L, Yin H, et al. The use of metformin and the incidence of lung cancer in patients with type 2 diabetes. Diabetes Care. 2013 Jan;36(1):124-9. PMID: 22923670.
No drug comparison of interest

Smiechowski BS, Suissa S, Azoulay L, et al. Metformin use and the incidence of colorectal cancer in patients with type 2 diabetes mellitus. Journal of Population Therapeutics and Clinical Pharmacology. 2012;19(2):e120.
Meeting abstract

Smirnov II, Zhuravlyova LV, Ilchenko IA. The minimal blood glucose variability is observed in type 2 diabetic patients on metformin plus DPP-IV inhibitors. Diabetologia. 2011;54((Smirnov I.I.; Zhuravlyova L.V.; Ilchenko I.A.) Internal Medicine No 3, Kharkov National Medical University, Ukraine):S340.
Meeting abstract

Smith CJ, Drummond RS. An observational analysis of the effect of incretin therapies in type 2 diabetes upon cardiovascular risk profiles. Diabetes, Stoffwechsel und Herz. 2011;20(6):431-2.
Meeting abstract

Smith CJ, Drummond RS. An observational study of the effect of incretin therapies upon cardiovascular risk in Type 2 diabetes. Diabetic Medicine. 2012;29((Smith C.J.; Drummond R.S.) Diabetes and Endocrinology, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom):15.
Meeting abstract

Soda S, Suzuki T, Matsubayashi Y. Alogliptin can be the first treatment choice in patients with untreated severe type 2 diabetes mellitus who require inpatient treatment. Diabetes. 2013;62((Soda S.; Suzuki T.; Matsubayashi Y.) Niigata, Japan):A673-A4.
Meeting abstract

Soffer D, Shi J, Chung J, et al. Does metformin use among women with type II diabetes reduce the risk of gynecologic cancers? International Journal of Gynecological Cancer. 2012;22((Soffer D.; Lentz S.) Gynecologic Oncology, Los Angeles, United States):E162.
Meeting abstract

Sohna Chandra Packiavathy A, Ramalingam M, Anchana Devi C. Role of pioglitazone on glycemic control and its effect on lipid profile in type 2 diabetics. Biomedical and Pharmacology Journal. 2010;3(1):07-10.
Placebo-controlled trial; No drug comparison of interest

Song KH, Kim JM, Noh JH, et al. Efficacy and Safety of Biphasic Insulin Aspart 30/70 in Type 2 Diabetes Suboptimally Controlled on Oral Antidiabetic Therapy in Korea: A Multicenter, Open-Label, Single-Arm Study (Diabetes Metab J 2013;37:117-24). Diabetes and Metabolism Journal. 2013;37(3):214-5.
No original data

Song XX, Jiang T, Kang K, et al. Efficacy of sitagliptin combined with metformin in the initial treatment of type 2 diabetes with non-alcoholic fatty liver. Chinese Journal of New Drugs. 2014;23(2):215-8+40.
Non-English language

Spanheimer R, Erdmann E, Song E, et al. Pioglitazone and bladder malignancy during observational follow-up of PROactive: 6-year update. Diabetologia. 2012;55((Spanheimer R.) Takeda Pharmaceuticals North America, Deerfield, United States):S324.
Meeting abstract

Spanheimer R, Zhao Z, Perez A. Effect of pioglitazone and metformin fixed-dose combination on glycemic control. Diabetes. 2009;58((Spanheimer R.; Zhao Z.; Perez A.) Deerfield, United States).
Meeting abstract

Spanheimer R, Zhao Z, Perez A. Evaluating effect of insulin resistance and beta cell function in a pioglitazone and metformin fixed-dose combination study. Diabetologia. 2009;52(S1):S212.
Meeting abstract

Spanheimer R, Zhao Z, Perez A. Evaluating effect of insulin resistance and ss-cell function in a pioglitazone and metformin fixed-dose combination study. Diabetes. 2009;58((Spanheimer R.; Zhao Z.; Perez A.) Deerfield, United States).
Meeting abstract

Spanheimer R, Zhao Z, Perez A. Improvement of glycaemic control via reducing insulin resistance with pioglitazone and metformin fixed-dose combination therapy. Canadian Journal of Diabetes. 2009;33(3):273.
Meeting abstract

Spinar J, Smahelova A. [SAVOR TIMI 53 - Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus]. Vnitr Lek. 2013 Nov;59(11):1003-7. PMID: 24279445.
No original data

Stafford S, Elahi D, Meneilly GS. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin in older adults with type 2 diabetes mellitus. Journal of the American Geriatrics Society; 2011. p. 1148-9.
Meeting abstract

Steinberg H, Engel SS, Golm GT, et al. Initial treatment with sitagliptin as monotherapy or combination therapy improves markers of (beta)-cell function in patients with type 2 diabetes. Diabetes. 2011;60((Steinberg H.; Engel S.S.; Golm G.T.; Alba M.; Langdon R.B.; Kaufman K.D.; Goldstein B.J.) Whitehouse Station, United States):A610.
Meeting abstract

Steinberg WM, Nauck MA, Zinman B, et al. LEADER 3-lipase and amylase activity in subjects with type 2 diabetes baseline data from over 9000 subjects in the LEADER trial. Pancreas. 2014;43(8):1223-31.
Background medications; No drug comparison of interest

Stenlof K, Bode B, Harris S, et al. Long-term efficacy and safety of canagliflozin in older patients with type 2 diabetes mellitus over 104 weeks. Diabetologia. 2014;57(1):S8-S9.
Meeting abstract

Stenlof K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin (CANA) monotherapy in subjects with type 2 diabetes mellitus (T2DM) over 52 weeks. Diabetes. 2013;62((Stenlof K.; Cefalu W.T.; Kim K.-A.; Jodar E.; Alba M.; Edwards R.; Tong C.; Canovatchel W.; Meininger G.) Gothenburg, Sweden, Baton Rouge, LA, Goyang, Republic of Korea, Madrid, Spain, Raritan, NJ):A303.
Meeting abstract

Stenlof K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise over 52 weeks. Diabetologia. 2013;56((Stenlof K.) Clinical Trial Center, Sahlgrenska University Hospital, Gothenburg, Sweden):S374.
Meeting abstract

Stenlof K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013 Apr;15(4):372-82. PMID: 23279307.
Background medications; No drug comparison of interest

Stenlof K, Cefalu WT, Tong C, et al. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, improves glycaemic control in subjects with type 2 diabetes

inadequately controlled with diet and exercise. Diabetologia. 2012;55((Stenlof K.) Clinical Trial Center, Sahlgrenska University Hospital, Gothenburg, Sweden):S312-S3.
Meeting abstract

Stephens JW, Fulcher G, Matthews DR, et al. Liraglutide add-on to metformin improves postprandial glucose control compared with metformin monotherapy in patients with Type 2 diabetes: Posthoc analysis of the Liraglutide Effect and Action in Diabetes (LEAD)2 study. Diabetic Medicine. 2014;31((Stephens J.W.) Endocrinology, College of Medicine, Swansea University, Swansea, United Kingdom):178.
Meeting abstract

Sterner G, Elmstahl S, Frid A. Renal function in a large cohort of metformin treated patients with type 2 diabetes mellitus. British Journal of Diabetes and Vascular Disease. 2012;12(5):227-31.
Does not meet study design criteria; No drug comparison of interest

Stewart MW, Reusch JEB, Bush MA, et al. Albiglutide, a long-acting GLP-1-receptor agonist, for the treatment of type 2 diabetes: An analysis of gastrointestinal adverse events over time. Diabetologia. 2009;52(S1):S302-S3.
Meeting abstract

Stewart MW, Reusch JEB, Bush MA, et al. The gastrointestinal adverse event profile of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes. Diabetes. 2009;58((Stewart M.W.; Reusch J.E.B.; Bush M.A.; Yang F.; Rosenstock J.)).
Meeting abstract

Stolar MW, Grimm M, Chen S. Comparison of extended release GLP-1 receptor agonist therapy versus sitagliptin in the management of type 2 diabetes. Diabetes Metab Syndr Obes. 2013;6:435-44. PMID: 24285927.
No original data

Stringer F, DeJongh J, Enya K, et al. Evaluation of the long-term durability and glycemic control of fasting plasma glucose and glycosylated hemoglobin for pioglitazone in Japanese patients with type 2 diabetes. Diabetes Technol Ther. 2015 Mar;17(3):215-23. PMID: 25531677.
Background medications; No drug comparison of interest

Strojek K, Hruba V, Elze M, et al. Efficacy and safety of dapagliflozin in patients with type 2 diabetes mellitus and inadequate glycaemic control on glimepiride monotherapy. Diabetologia. 2010;53((Strojek K.) Silesian Medical University, Zabrze, Poland):S347-S8.
Meeting abstract

Strojek K, Yoon KH, Hruba V, et al. Dapagliflozin added to glimepiride in patients with type 2 diabetes mellitus sustains glycemic control and weight loss over 48 weeks: a randomized, double-blind, parallel-group, placebo-controlled trial. Diabetes Ther. 2014 Jun;5(1):267-83. PMID: 24920277.
Meeting abstract

Strongman H, D'Oca K, Langerman H, et al. A comparison of diabetes-associated secondary healthcare utilisation between alternative oral anti-hyperglycaemic dual therapy combinations with metformin in patients with type 2 diabetes: an observational cohort study. Diabetes Obes Metab. 2015 Mar 4PMID: 25735201.
Background medications

Strongman H, D'Oca K, Langerman H, et al. Comparison of diabetes-associated

secondary healthcare utilization between alternative oral antihyperglycaemic dual therapy combinations with metformin in patients with type 2 diabetes: an observational cohort study. Diabetes Obes Metab. 2015 Jun;17(6):573-80. PMID: 25735201.
No drug comparison of interest; Does not report long-term outcomes or adverse events

Stull DE, Houghton K, Traina SB. Growth mixture modeling (GMM) to determine treatment effects of canagliflozin versus sitag liptin on weight-related quality of life (WRQoL) in subjects with type 2 diabetes mellitus (T2DM). Value in Health. 2013;16(7):A447.
Meeting abstract

Subrahmanyam BS, Bhava BSS, Venkateshwarlu E, et al. Efficacy of oral anti-diabetic agents for glycaemic control in type-2 diabetic patients with obesity. Global Journal of Pharmacology. 2013;7(3):311-5.
Does not meet study design criteria

Succurro E, Ruffo M, Cutruzzola A, et al. Weight reduction and cardiometabolic control in diabetic patients treated with liraglutide or sitagliptin, both in association with metformin. Eating and Weight Disorders. 2014;19(3):452.
Meeting abstract

Succurro E, Ruffo MF, Lugara M, et al. Weight reduction and cardiometabolic control in diabetic patients treated with liraglutide or sitagliptin, both in association with metformin. High Blood Pressure and Cardiovascular Prevention. 2013;20(2):109.
Meeting abstract

Sudhakaran C, Fathima M, Anjana RM, et al. Effectiveness of exenatide in Asian Indians in a clinical care setting. Diabetes Technol Ther. 2010 Aug;12(8):613-8. PMID: 20615102.
Background medications

Sudhakaran C, Kishore U, Anjana RM, et al. Effectiveness of sitagliptin in asian Indian patients with type 2 diabetes-an Indian tertiary diabetes care center experience. Diabetes Technol Ther. 2011 Jan;13(1):27-32. PMID: 21175268.
Background medications

Suh DC, Lee DH, McGuire M, et al. Impact of rosiglitazone therapy on the lipid profile, glycemic control, and medication costs among type 2 diabetes patients. Curr Med Res Opin. 2011 Aug;27(8):1623-33. PMID: 21696266.
No drug comparison of interest; Background medications

Sultana SS, Amin F, Rahman A, et al. A comparative study with metformin and pioglitazone versus metformin alone in nonalcoholic fatty liver disease in newly detected glucose intolerant patients. Diabetologia. 2012;55((Sultana S.S.; Amin F.; Rahman A.; Afsana F.) BIRDEM, Dhaka, Bangladesh):S500.
Meeting abstract

Sun GE, Wells BJ, Yip K, et al. Gender-specific effects of oral hypoglycaemic agents on cancer risk in type 2 diabetes mellitus. Diabetes Obes Metab. 2014 Mar;16(3):276-83. PMID: 24199848.
Background medications

Sun SX, Vallarino C, Xu Y, et al. Risk of stroke or myocardial infarction of t2dm patients treated with pioglitazone or non-thiazolidinedione in a managed care setting in the United States. Value in Health. 2009;12(7):A234-A5.
Meeting abstract

Suraj B, Tripathi CD, Biswas K, et al. A Comparative Evaluation of Safety, Efficacy and Cost Effectiveness of Three Add on Treatment Regimens in Type 2 Diabetics; Not Controlled by Metformin Alone. Research Journal of Pharmacy and Technology. 2015;8(1):44-50.
Meeting abstract

Suzuki K. Quantifying the effect of metformin 1000 mg/day in japanese patients with type 2 diabetes mellitus. Therapeutic Research. 2015;36(1):69-76.
Non-English language

Svacina S, Vesela V. [Prospective, multicentric, non-interventional study to assess the existing treatment of type 2 diabetes mellitus patients inadequately controlled with metformin monotherapy - KOMETA CZ]. Vnitr Lek. 2013 Dec;59(12):1043-8. PMID: 24350935.
Does not account for confounding; No drug comparison of interest

Swinnen SGH, Dain MP, Aronson R, et al. Once-daily insulin glargine requires a significantly lower dose than insulin detemir twice daily to achieve good glycaemic control in patients with type 2 diabetes failing oral therapy. Diabetologia. 2009;52(S1):S380.
Meeting abstract

Swislocki ALM, Meier JL, Najera SM, et al. Long-Term maintenance of glucose control in veterans with type 2 diabetes mellitus using oral agents. Metabolic Syndrome and Related Disorders. 2011;9(6):469-73.
Background medications; No drug comparison of interest

T MJ, Saha K, Steinberg W. Assessment of acute pancreatitis in liraglutide type 2 diabetes trials. Pancreas. 2012;41(8):1370-1.
Meeting abstract

Tahbaz A, Jones R, Sapin H, et al. Exenatide twice daily versus insulin glargine in the HEELA (Helping Evaluate Exenatide Compared with Long-acting Insulin) study in Type 2 diabetes: Evaluation of treatment-emergent nausea and changes in body weight. Diabetic Medicine. 2011;28((Tahbaz A.; Jones R.; Baguley J.) Medical Department, Eli Lilly and Company, Basingstoke, United Kingdom):70.
Meeting abstract

Tahrani AA. SGLT-2 inhibitors as second-line therapy in type 2 diabetes. Lancet Diabetes Endocrinol. 2014 Jun 16PMID: 24948512.
No original data

Tajiri Y, Tsuruta M, Ohki T, et al. Long-term efficacy of sitagliptin for the treatment of type 2 diabetic patients in Japan. Endocr J. 2012;59(3):197-204. PMID: 22156327.
No drug comparison of interest

Takagi T, Okura H, Kobayashi Y, et al. A prospective, multicenter, randomized trial to assess efficacy of pioglitazone on in-stent neointimal suppression in type 2 diabetes: POPPS (Prevention of In-Stent Neointimal Proliferation by Pioglitazone Study). JACC Cardiovasc Interv. 2009 Jun;2(6):524-31. PMID: 19539256.
Background medications; Comorbidity

Takai M, Ishikawa M, Maeda H, et al. Safety and efficacy of adding sitagliptin to insulin in patients with type 2 diabetes: the ASSIST-K study. Diabetes Res Clin Pract. 2014 Mar;103(3):e30-3. PMID: 24525293.
No drug comparison of interest

Takayuki Fujiwara T, Yoshida M, Nakamura T, et al. Administration of dipeptidyl peptidase-4 inhibitors is

associated with improvement of left ventricular diastolic function after acute myocardial infarction in diabetic patients. European Journal of Heart Failure. 2014;16((Takayuki Fujiwara T.; Yoshida M.; Nakamura T.; Umemoto T.; Funayama H.; Sugawara Y.; Mitsuhashi T.; Kakei M.; Momomura M.; Ako J.) Jichi Medical University, Saitama Medical Center, Saitama, Japan):164.
Meeting abstract

Takihata M, Nakamura A, Tajima K, et al. Comparative study of sitagliptin with pioglitazone for strict glycemic control: The compass study. Diabetes. 2012;61((Takihata M.; Nakamura A.; Tajima K.; Inazumi T.; Komatsu Y.; Tamura H.; Yamazaki S.; Kondou Y.; Yamada M.; Kimura M.; Terauchi Y.) Yokohama, Kanagawa, Japan):A256.
Meeting abstract

Takihata M, Nakamura A, Tajima K, et al. Comparative study of sitagliptin with pioglitazone in Japanese type 2 diabetic patients: the COMPASS randomized controlled trial. Diabetes Obes Metab. 2013 May;15(5):455-62. PMID: 23279373.
Background medications

Tamblyn R, Abrahamowicz M, Beauchamp ME, et al. International pharmacosurveillance: Modeling exposure to diabetic drugs in relationship to cardiovascular effects. Pharmacoepidemiology and Drug Safety. 2013;22((Tamblyn R.; Girard N.) Medicine, McGill University, Montreal, Canada):182.
Meeting abstract

Tamez-Perez HE. [Efficacy and safety of initial treatment with glimpeiride versus sitagliptin in type 2 diabetes]. Rev Med Inst Mex Seguro Soc. 2015 Mar-Apr;53(2):142-8. PMID: 25760742.
Non-English language

Tamir O, Wainstein J, Raz I, et al. Treatment modality, quality of life, and patient-perceived difficulties in the treatment of diabetes. Review of Diabetic Studies. 2012;9(1).
No drug comparison of interest

Tamita K, Okura H, Takagi T, et al. Impact of in-stent neointimal suppression by pioglitazone on clinical outcome in type 2 diabetes: 5-year follow-up of the prevention of neointimal proliferation by pioglitazone study. EuroIntervention. 2013;9((Tamita K.; Yoshikawa J.) Nishinomiya Watanabe Cardiovascular Center, Nishinomiya, Japan):16.
Meeting abstract

Tarbett AK, VanRoekel RC, Howard RS, et al. The use of optical coherence tomography to determine the effect of thiazolidinediones on retinal thickness in patients with type 2 diabetes. J Diabetes Sci Technol. 2011 Jul;5(4):945-51. PMID: 21880238.
No drug comparison of interest

Tasic D, Brixner D, Goodman M. The impact of oral antidiabetics on weight in the elderly with type 2 diabetes mellitus in the ambulatory setting. Value in Health. 2010;13(3):A54-A5.
Meeting abstract

Tatosian DA, Guo Y, Schaeffer AK, et al. Dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes treated with saxagliptin, sitagliptin, or vildagliptin. Diabetes Ther. 2013 Dec;4(2):431-42. PMID: 24163113.
Follow-up less than 3 months

Teigland C, Parente A, Mehta S, et al. Comparative effectiveness of sulfonylurea and metformin on risk of cardiac events in middle-aged adults with type II diabetes

mellitus. Diabetes. 2013;62((Teigland C.; Parente A.; Mehta S.; Jones B.; Chen P.; Scoggins J.) Bowie, United States):A373.
Meeting abstract

Terauchi Y, Satoi Y, Takeuchi M, et al. Monotherapy with the once weekly GLP-1 receptor agonist dulaglutide for 12 weeks in Japanese patients with type 2 diabetes: dose-dependent effects on glycaemic control in a randomised, double-blind, placebo-controlled study. Endocr J. 2014;61(10):949-59. PMID: 25029955.
Placebo-controlled trial

Tharp WG, Sideleva O, Elahi D, et al. Pioglitazone (PIO) does not enhance glucose-dependent insulinotropic peptide (GIP) stimulated insulin secretion in subjects with well-controlled t2dm. Diabetes. 2011;60((Tharp W.G.; Sideleva O.; Elahi D.; Ledger C.; Maple R.; Pratley R.) Burlington, United States):A444.
Meeting abstract

Tharp WG, Sideleva O, Maple RL, et al. Independent increases in insulin sensitivity and adipocyte GIP-R expression following pioglitazone (PIO) treatment in patients with type 2 diabetes mellitus (T2DM). Obesity. 2011;19((Tharp W.G.; Sideleva O.; Maple R.L.; Pratley R.) Colchester, United States):S181.
Meeting abstract

The LEAD study program - Liraglutide: Glycemic control with weight reduction. MMW-Fortschritte der Medizin. 2009;151(26-29):7-8.
Meeting abstract

Thomas J. Addition of linagliptin to metformin improves glycaemic control in type 2 diabetes. Australian Journal of Pharmacy. 2012;93(1110):97.
No original data

Thong KY, Jose B, Sukumar N, et al. Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit. Diabetes, Obesity and Metabolism. 2011;13(8):703-10.
No drug comparison of interest

Thong KY, Gupta PS, Blann AD, et al. The influence of age and metformin treatment status on reported gastrointestinal side effects with liraglutide treatment in type 2 diabetes. Diabetes Res Clin Pract. 2015 Jul;109(1):124-9. PMID: 25937541.
Background medications; No comparison of interest

Thrasher J, Daniels K, Patel S, et al. Black/African American patients with type 2 diabetes mellitus: study design and baseline patient characteristics from a randomized clinical trial of linagliptin. Expert Opin Pharmacother. 2012 Dec;13(17):2443-52. PMID: 23134211.
No original data; Background medications

Thrasher J, Daniels K, Patel S, et al. Efficacy and Safety of Linagliptin in Black/African American Patients with Type 2 Diabetes: A 6-month, Randomized, Double-blind, Placebo-controlled Study. Endocr Pract. 2014 May 1;20(5):412-20. PMID: 24326003.
No drug comparison of interest; Placebo-controlled trial

Tikkanen I, Narko K, Zeller C, et al. Empagliflozin improves 24-hour blood pressure profiles in patients with type 2 diabetes and hypertension. Circulation. 2013;128(22).
Meeting abstract

Tikkanen I, Narko K, Zeller C, et al. Empagliflozin improves blood pressure in patients with type 2 diabetes (T2DM) and hypertension. Giornale Italiano di Cardiologia. 2014;15(4):e54.
Meeting abstract

Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. Diabetes Care. 2015 Mar;38(3):420-8. PMID: 25271206.
Placebo-controlled trial; No drug comparison of interest

Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces blood pressure in patients with Type 2 diabetes and hypertension: A phase III, randomised, double-blind, placebo-controlled trial (EMPA-REG BP(trademark)). Diabetic Medicine. 2014;31((Tikkanen I.) Department of Medicine, Helsinki University Central Hospital, Minerva Institute for Medical Research, Helsinki, Finland):64.
Meeting abstract

Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces blood pressure in patients with Type 2 diabetes and hypertension: A phase III, randomised, double-blind, placebo-controlled trial (EMPA-REG BP). Diabetic Medicine; 2014. p. 64, Abstract no: LB-OR02-6.
Meeting abstract

Timofte L, Stratmann B, Quester W, et al. Exenatide and liraglutide - Side effects. Comparative clinical study. Farmacia. 2013;61(5):837-44.
Does not account for confounding; Background medications

Timofte L, Stratmann B, Bojita MT, et al. Global view on safety and efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: The study shows data from clinical routine use in a cohort of patients with type 2 diabetes mellitus. Diabetes, Stoffwechsel und Herz. 2015;24(1):19-27.
Background medications; Does not account for confounding

Tinahones FJ, Gomez-Huelgas R, Garciaalegria J, et al. The effect of insulin detemir on fat distribution and weight parameters in overweight and obese subjects with type 2 diabetes. Diabetes. 2011;60((Tinahones F.J.; Gomez-Huelgas R.; Garciaalegria J.; Tapia-Guerrero M.J.; Perez F.M.) Malaga, Spain):A309.
Meeting abstract

Tofe Povedano S, Dungan KM, Forst T, et al. Efficacy and safety of once weekly dulaglutide versus once daily liraglutide in type 2 diabetes (AWARD6). Diabetologia. 2014;57(1):S23.
Meeting abstract

Tofe Povedano S, Umpierrez G, Perez Manghi F, et al. Efficacy and safety of dulaglutide vs metformin in type 2 diabetes (AWARD-3). Diabetologia. 2013;56((Tofe Povedano S.) Endocrinologia, Clinica Juaneda, Palma de Mallorca, Spain):S8.
Meeting abstract

Tomasetti PE, Lubbers HT, Lanzer M, et al. Metformin and oral squamous cell carcinoma? Head and Neck Oncology. 2014;6(2).
Meeting abstract

Toubro S, Cefalu WT, Xie J, et al. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, reduces body weight mainly through loss of fat mass in subjects with type 2 diabetes. Diabetologia. 2012;55((Toubro S.) Reduce, A Research Clinic, Vipperod, Denmark):S313-S4.

Meeting abstract

Traina S, Guthrie R, Slee A. The impact of weight loss on weight-related quality of life and health satisfaction: results from a trial comparing canagliflozin with sitagliptin in triple therapy among people with type 2 diabetes. Postgrad Med. 2014 May;126(3):7-15. PMID: 24918788.
No drug comparison of interest

Traina S, Slee A, Neslusan C. Impact of weight loss on weight-related quality of life (WRQL) and health satisfaction (HS): Evidence from a head-to-head study of canagliflozin (CANA) vs sitagliptin (SITA). Diabetologia. 2014;57(1):S335.
Meeting abstract

Traina SB, Ho KF. Weight- and health-related quality of life (WRQoL and HRQoL) with canagliflozin (CANA) versus sitagliptin (SITA) in subjects with type 2 diabetes mellitus (T2DM) on background metformin. Value in Health. 2013;16(7):A448.
Meeting abstract

Traina SB, Neslusan C, Slee A. The association of health-related quality of life (HRQOL) and achievement of disease management goals in the treatment of type 2 diabetes mellitus (T2DM). Value in Health. 2014;17(3):A257.
Meeting abstract

Trautmann M, Giaconia J, Choi S. Impact of exenatide twice daily on body weight in different patient groups. Diabetic Medicine. 2011;28((Trautmann M.; Giaconia J.; Choi S.) Eli Lilly and Company, Indianapolis, United States):72-3.
Meeting abstract

Trautmann ME, Malloy J, Han J. Sustained glycaemic control with exenatide once weekly versus insulin glargine: Associations with baseline factors and early treatment response. Diabetologia. 2014;57(1):S343.
Meeting abstract

Tremblay AJ, Lamarche B, Deacon CF, et al. Effect of sitagliptin therapy on postprandial lipoprotein levels in patients with type 2 diabetes. Diabetes Obes Metab. 2011 Apr;13(4):366-73. PMID: 21226820.
Follow-up less than 3 months; No outcome of interest

Tschope D, Bramlage P, Binz C, et al. Antidiabetic pharmacotherapy and anamnestic hypoglycemia in a large cohort of type 2 diabetic patients--an analysis of the DiaRegis registry. Cardiovasc Diabetol. 2011;10:66. PMID: 21756359.
Does not account for confounding; Does not meet study design criteria

Tschope D, Bramlage P, Binz C, et al. DPP-4 inhibitors versus sulfonylureas on top of metformin in a real world setting-Results of 1 year follow-up of the prospective diaregis registry. Diabetes. 2012;61((Tschope D.; Bramlage P.; Binz C.; Krekler M.; Lobner K.; Deeg E.; Gitt A.K.) Bad Oeynhausen, Germany):A282.
Meeting abstract

Tschope D, Bramlage P, Binz C, et al. Incidence, characteristics, and impact of hypoglycemia in type 2 diabetic patients with intensified glycaemic control in clinical practice-2-year prospective follow-up of the diaregis cohort study. Diabetes. 2014;63((Tschope D.; Bramlage P.; Binz C.; Krekler M.; Gitt A.K.) Bad Oeynhausen, Germany, Mahlow, Germany, Munich, Germany, Ludwigshafen, Germany):A380.
Meeting abstract

Tschope D, Bramlage P, Binz C, et al. Predictors of hypoglycemia in patients with

type-2 diabetes-An analysis of the prospective diaregis registry. Diabetes. 2012;61((Tschope D.; Bramlage P.; Binz C.; Krekler M.; Lobner K.; Deeg E.; Gitt A.K.) Bad Oeynhausen, Germany):A554.
Meeting abstract

Tseng CH. Diabetes, metformin use, and colon cancer: a population-based cohort study in Taiwan. Eur J Endocrinol. 2012 Sep;167(3):409-16. PMID: 22778198.
No drug comparison of interest; Backgrounf medications

Tseng CH. Metformin may reduce bladder cancer risk in Taiwanese patients with type 2 diabetes. Acta Diabetol. 2014 Apr;51(2):295-303. PMID: 24509842.
Background medications

Tseng CH. Metformin may reduce breast cancer risk in Taiwanese women with type 2 diabetes. Breast Cancer Res Treat. 2014 Jun;145(3):785-90. PMID: 24816805.
No drug comparison of interest; Background medications

Tseng CH. Metformin significantly reduces incident prostate cancer risk in Taiwanese men with type 2 diabetes mellitus. Eur J Cancer. 2014 Nov;50(16):2831-7. PMID: 25201464.
No drug comparison of interest

Tseng CH. Pioglitazone and bladder cancer: a population-based study of Taiwanese. Diabetes Care. 2012 Feb;35(2):278-80. PMID: 22210574.
No drug comparison of interest

Tseng CH. Pioglitazone and thyroid cancer risk in taiwanese patients with type 2 diabetes. Journal of Diabetes. 2014((Tseng C.-H., ccktsh@ms6.hinet.net) Department of Internal Medicine National Taiwan University College of Medicine Taipei, Taiwan).
No drug comparison of interest; Background medications

Tseng CH. Pioglitazone does not affect the risk of kidney cancer in patients with type 2 diabetes. Metabolism. 2014 May 6PMID: 24889868.
No drug comparison of interest

Tseng CH. Pioglitazone does not affect the risk of ovarian cancer: analysis of a nationwide reimbursement database in Taiwan. Gynecol Oncol. 2013 Oct;131(1):135-9. PMID: 23877016.
No drug comparison of interest

Tseng CH. Rosiglitazone may reduce non-melanoma skin cancer risk in Taiwanese. BMC Cancer. 2015 Feb 6;15(1):41. PMID: 25655946.
No type 2 diabetes; Background medications

Tseng CH. Rosiglitazone may reduce thyroid cancer risk in patients with type 2 diabetes. Ann Med. 2013 Dec;45(8):539-44. PMID: 24215589.
No drug comparison of interest; Background medications

Tsilidis KK, Capothanassi D, Allen N, et al. Metformin and cancer risk: A cohort study in the UK Clinical Practice Research Datalink analyzed like a randomized trial. Cancer Research. 2014;74(19).
Meeting abstract

Tsilidis KK, Capothanassi D, Allen NE, et al. Metformin Does Not Affect Cancer Risk: A Cohort Study in the U.K. Clinical Practice Research Datalink Analyzed Like an Intention-to-Treat Trial. Diabetes Care. 2014 Jun 4PMID: 24898303.
Does not account for confounding

Tsuchiya M, Nishio Y, Maegawa H. Long-term effect of DPP4 inhibition on dyslipidemia and the size of LDL particles in patients with IGT or type 2 diabetes. Diabetes. 2012;61((Tsuchiya M.) Yanai, Japan):A577.
Meeting abstract

Tziomalos K, Bouziana S, Pavlidis A, et al. Prior treatment with dipeptidyl-peptidase IV inhibitors is associated with favorable outcome in patients with acute ischemic stroke. Diabetes. 2013;62((Tziomalos K.; Bouziana S.; Pavlidis A.; Spanou M.; Giampatzis V.; Papadopoulou M.; Giannakidou F.; Iliadis F.; Didangelos T.; Savopoulos C.; Hatzitolios A.) Thessaloniki, Greece):A312.
Meeting abstract

Tzoulaki I, Molokhia M, Curcin V, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ. 2009;339:b4731. PMID: 19959591.
Does not meet study design criteria

Udell JA, Scirica B, Cavender MA, et al. Baseline renal function and cardiovascular risk in patients treated with saxagliptin: Observations from the savor-TIMI 53 trial. Journal of the American College of Cardiology. 2014;63(12):A1523.
Meeting abstract

Uhl D. Type 2 diabetes: Vitamin B12 level drops with the use of metformin. Deutsche Apotheker Zeitung. 2010;150(24):32-3.
Meeting abstract

Uhlig-Laske B, Ring A, Graefe-Mody U, et al. Linagliptin, a potent and selective DPP-4 inhibitor, is safe and efficacious in patients with inadequately controlled type 2 diabetes despite metformin therapy. Diabetes. 2009;58((Uhlig-Laske B.; Ring A.; Graefe-Mody U.; Friedrich C.; Herbach K.; Woerle H.-J.; Dugi K.A.) Biberach, Germany).
Meeting abstract

Umetsu R, Nishibata Y, Abe J, et al. [Evaluation of the association between the use of oral anti-hyperglycemic agents and hypoglycemia in Japan by data mining of the Japanese Adverse Drug Event Report (JADER) database]. Yakugaku Zasshi. 2014;134(2):299-304. PMID: 24492232.
Does not account for confounding

Umpierrez G, Atkin S, Bain S, et al. Efficacy and safety of liraglutide versus placebo in subjects with type 2 diabetes and moderate renal impairment (LIRA-RENAL): A randomised trial. Diabetologia. 2014;57(1):S84.
Meeting abstract

Umpierrez G, Blevins T, Rosenstock J, et al. Effect of LY2189265, a long-acting glucagon-like peptide 1 analog, on metabolic outcomes and GI events in obese patients with uncontrolled type 2 diabetes mellitus (T2DM): The EGO study. Canadian Journal of Diabetes. 2009;33(3):210.
Meeting abstract

Umpierrez G, Blevins T, Rosenstock J, et al. Titration effect of LY2189265 (GLP-1 Analog) once weekly on metabolic outcomes and gi events in uncontrolled type 2 diabetes Mellitus (T2DM): The ego study. Diabetes. 2009;58((Umpierrez G.; Blevins T.; Rosenstock J.; Cheng C.; Bastyr E.; Anderson J.)):LB4.
Meeting abstract

Umpierrez GE, Blevins T, Rosenstock J, et al. The effects of LY2189265, a long-acting glucagon-like peptide-1 analogue, in a

randomized, placebo-controlled, double-blind study of overweight/obese patients with type 2 diabetes: The EGO study. Diabetes, Obesity and Metabolism. 2011;13(5):418-25.
No drug comparison of interest

Umpierrez GE, Manghi FP, Povedano ST, et al. Efficacy and safety of dulaglutide vs. Metformin in type 2 diabetes (AWARD-3). Diabetes. 2013;62((Umpierrez G.E.; Manghi F.P.; Povedano S.T.; Shurzinske L.; Pechtner V.) Atlanta, GA, Buenos Aires, Argentina, Palma de Mallorca, Spain, Indianapolis, IN, Suresnes, France):A17.
Meeting abstract

Umpierrez GE, Zhang Q, Rosenstock J. One-year rate of hospitalization following initiation of insulin glargine or exenatide in patients with type 2 diabetes. Diabetes. 2009;58((Umpierrez G.E.; Zhang Q.; Rosenstock J.)).
Meeting abstract

Upahyay RY, Cortes GA, Tun H, et al. Effect of diabetes mellitus treatment type in patients undergoing percutaneous coronary intervention. Circulation. 2012;126(21).
ur Rahman I, Idrees M, Salman M, et al. A comparison of the effect of glitazones on serum sialic acid in patients with type 2 diabetes. Diab Vasc Dis Res. 2012 Jul;9(3):238-40. PMID: 22067722.
Meeting abstract

Urquhart BS. Comparing incretin-based therapies. Evaluating GLP-1 agonists and DPP-4 inhibitors for type 2 diabetes mellitus. Adv NPs PAs. 2010 Oct;1(2):38-44. PMID: 21299149.
No original data

Usiskin K, Kline I, Fung A, et al. Safety and tolerability of canagliflozin in patients with type 2 diabetes mellitus: pooled Analysis of Phase 3 Study Results. Postgrad Med. 2014 May;126(3):16-34. PMID: 24918789.
Handsearch

Usiskin K, Leiter LA, Forst T, et al. Effect of canagliflozin (CANA) on liver function tests (LFTS) in patients with type 2 diabetes mellitus (T2DM). Diabetes. 2014;63((Usiskin K.; Leiter L.A.; Forst T.; Polidori D.; Xie J.; Sha S.) Raritan, NJ, Toronto, ON, Canada, Mainz, Germany, San Diego, CA):A284.
Meeting abstract

Valensi P, De Pouvourville G, Benard N, et al. Duration of maintenance of dual therapy with metformin and sitagliptin in type 2 diabetes: The Odyssee observational study. Diabetologia. 2014;57(1):S367.
Meeting abstract

Valentine WJ, Palmer AJ, Lammert M, et al. Evaluating the long-term cost-effectiveness of liraglutide versus exenatide BID in patients with type 2 diabetes who fail to improve with oral antidiabetic agents. Clin Ther. 2011 Nov;33(11):1698-712. PMID: 22018679.
No original data; Background medications

Van Brunt K, Reaney M, Yu M, et al. Patient-reported outcomes with dulaglutide, exenatide, or placebo (AWARD-1). Diabetologia. 2013;56((Van Brunt K.; Reaney M.) Eli Lilly, Surrey, United Kingdom):S394-S5.
Meeting abstract

van Dieren S, Czernichow S, Chalmers J, et al. Weight changes and their predictors amongst 11 140 patients with type 2 diabetes in the ADVANCE trial. Diabetes Obes Metab. 2012 May;14(5):464-9. PMID: 22226008.
Background medications

Van Dieren S, Kengne AP, Chalmers J, et al. Weight changes and their predictors among 11,140 patients with type 2 diabetes in the advance trial. Circulation. 2012;125(10).
Meeting abstract

Varewijck AJ, Janssen JA, Vahatalo M, et al. Addition of insulin glargine or NPH insulin to metformin monotherapy in poorly controlled type 2 diabetic patients decreases IGF-I bioactivity similarly. Diabetologia. 2012 Apr;55(4):1186-94. PMID: 22237688.
No original data

Varewijck AJ, Janssen JAMJL, Vahatalo M, et al. IGF-I bioactivity decreases during insulin therapy in type 2 diabetic patients: Comparison of high doses of insulin glargine and nph insulin in the lanmet study. Endocrine Reviews. 2011;32(3).
Meeting abstract

Vel S, Frid A, Hermansen K, et al. Evaluation of patient-reported outcomes in subjects with Type 2 diabetes treated with the once-daily human GLP-1 analogue liraglutide or glimepiride, both as addon to metformin. Diabetic Medicine. 2009;26((Vel S.) Novo Nordisk UK, Crawley, United Kingdom):145-6.
Meeting abstract

Venskutonyte L, Brismar K, Ryden-Bergsten T, et al. Satisfaction with glucose-lowering treatment and well-being in patients with type 2 diabetes and myocardial infarction: A DIGAMI2 QoL sub-study. Diabetes and Vascular Disease Research. 2013;10(3):263-9.
No drug comparison of interest

Vichayanrat A, Matawaran BJ, Wibudi A, et al. Assessment of baseline characteristics, glycemic control and oral antidiabetic treatment in Asian patients with diabetes: The Registry for Assessing OAD Usage in Diabetes Management (REASON) Asia study. J Diabetes. 2013 Sep;5(3):309-18. PMID: 23462227.
No drug comparison of interest; Background medications

Vilar L, Canadas V, Arruda MJ, et al. Comparison of metformin, gliclazide MR and rosiglitazone in monotherapy and in combination for type 2 diabetes. Arq Bras Endocrinol Metabol. 2010 Mar;54(3):311-8. PMID: 20520962.
Does not account for confounding

Viljoen A, Meek CL, Gadsby R, et al. Efficacy and safety of DPP-IV inhibitors for the treatment of older people with Type 2 diabetes: An observational study. Diabetic Medicine. 2013;30((Viljoen A.; Viljoen S.; Langerman C.; Sinclair A.) Institute of Diabetes for Older People, University of Bedfordshire, Luton, United Kingdom):165.
Meeting abstract

Viljoen A, Meek CL, Gadsby R, et al. The tolerability and safety of DPP-4 inhibitors for the treatment of older people with type 2 diabetes mellitus: An observational study. British Journal of Diabetes and Vascular Disease. 2013;13(4):187-91.
Background medications; No drug comparison of interest

Villena JE, Yoshiyama CA, Sanchez JE, et al. Prevalence of diabetic retinopathy in Peruvian patients with type 2 diabetes: results of a hospital-based retinal telescreening program. Rev Panam Salud Publica. 2011 Nov;30(5):408-14. PMID: 22262266.
Does not account for confounding; Background medications

Viney T, Blackmore M, Shaww N, et al. Positive experiences of starting exenatide

inpatients with Type 2 diabetes in a busy diabetic clinic. Diabetic Medicine. 2009;26((Viney T.; Blackmore M.; English P.; Millward A.) Diabetes Clinical Research Centre, Plymouth Diabetes Centre, Derriford, United Kingdom):139.
Meeting abstract

Vinik AI, Cincotta AH, Scranton RE, et al. Effect of bromocriptine-QR on glycemic control in subjects with uncontrolled hyperglycemia on one or two oral anti-diabetes agents. Endocr Pract. 2012 Nov-Dec;18(6):931-43. PMID: 23186965.
No drug comparison of interest

Virdi NS, Raja P, Daskiran M, et al. Association of SMBG with medication adherence and glycemic control. Diabetes. 2011;60((Virdi N.S.; Raja P.; Daskiran M.; Kozma C.; Nigam S.) Milpitas, United States):A66.
Meeting abstract

Von Eynatten M, Gong Y, Emser A, et al. Safety and Efficacy of Linagliptin in Type 2 Diabetes (T2D) Patients with Common Renal and Cardiovascular Risk Factors. Endocr Rev. 2012;33(3).
Meeting abstract

Vora J, Malloy J, Zhou M, et al. Daily blood glucose variability with exenatide once weekly versus basal insulin in 3 randomised controlled trials. Diabetologia. 2014;57(1):S343.
Meeting abstract

Wahlqvist ML, Lee MS, Chuang SY, et al. Increased risk of affective disorders in type 2 diabetes is minimized by sulfonylurea and metformin combination: a population-based cohort study. BMC Med. 2012;10:150. PMID: 23194378.
No outcome of interest

Wahlqvist ML, Lee MS, Hsu CC, et al. Metformin-inclusive sulfonylurea therapy reduces the risk of Parkinson's disease occurring with Type 2 diabetes in a Taiwanese population cohort. Parkinsonism Relat Disord. 2012 Jul;18(6):753-8. PMID: 22498320.
Does not apply

Wainstein J, Katz L, Engel SS, et al. Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycaemic control compared with pioglitazone monotherapy in patients with type 2 diabetes. Diabetes Obes Metab. 2012 May;14(5):409-18. PMID: 22059736.
No drug comparison of interest

Walton C, Ryder REJ, Cull ML, et al. Factors associated with HbA1c and weight changes at 6 months in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide and liraglutide audit. Diabetologia. 2011;54((Walton C.) Diabetes, Hull Royal Infirmary, Birmingham, United Kingdom):S326-S7.
Meeting abstract

Walton C, Ryder REJ, Cull ML, et al. Factors associated with HbA1c and weight changes at 6 months in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide and liraglutide audit. Practical Diabetes. 2012;29(3):124d-e.
Meeting abstract

Wang CC, Chen WL, Kao TW, et al. Incidence of cardiovascular events in which 2 thiazolidinediones are used as add-on treatments for type 2 diabetes mellitus in a Taiwanese population. Clin Ther. 2011 Dec;33(12):1904-13. PMID: 22118894.
Background medications

Wang MM, Lin S, Chen YM, et al. Saxagliptin is similar in glycaemic

variability more effective in metabolic control than acarbose in aged type 2 diabetes inadequately controlled with metformin. Diabetes Res Clin Pract. 2015 Jun;108(3):e67-70. PMID: 25841300.
Does not account for confounding

Wang W, Yang J, Yang G, et al. Efficacy and safety of linagliptin in Asian patients with type 2 diabetes mellitus inadequately controlled on metformin: A 24-week, randomized, phase III clinical trial. Diabetes. 2013;62((Wang W.; Yang J.; Yang G.; Gong Y.; Woerle H.-J.; Ning G.) Shanghai, China, Beijing, China, Chongqing, China, Ingelheim, Germany):A307.
Meeting abstract

Wangnoo SK, Mithal A, Kumar S, et al. Safety and efficacy of liraglutide in type 2 diabetes: Post marketing surveillance data from India. Diabetologia. 2012;55((Wangnoo S.K.; Mithal A.) Dept. of Endocrinology, Indraprastha Apollo Hospital, New Delhi, India):S299.
Meeting abstract

Ways K, Nyirjesy P, Sobel JD, et al. Genital mycotic infections with canagliflozin in subjects with type 2 diabetes mellitus. Diabetologia. 2013;56((Ways K.; Fung A.; Usiskin K.) Janssen Research and Development, LLC, Raritan, United States):S381.
Meeting abstract

Weber MA, List J, Mansfield TA, et al. Combined hba1c and systolic blood pressure reduction with dapagliflozin in patients with both inadequately controlled type 2 diabetes mellitus and hypertension. Circulation. 2014;130((Weber M.A.) Internal Medicine, SUNY Downstate College of Medicine, New York, United States).
Meeting abstract

Weber MA, Mansfield TA, Alessi F, et al. Effects of dapagliflozin on blood pressure in diabetic patients with hypertension inadequately controlled by a renin-angiotensin system blocker. Circulation. 2013;128(22).
Meeting abstract

Weber MA, Mansfield TA, Iqbal N, et al. Dapagliflozin lowers HbA1c, systolic blood pressure and serum uric acid in patients with type 2 diabetes and hypertension, regardless of class of concomitant antihypertensive therapy. Circulation. 2014;130((Weber M.A.) Internal Medicine, SUNY Downstate College of Medicine, New York, United States).
Meeting abstract

Weber MA, Mansfield TA, T'Joen C, et al. Dapagliflozin for reduction of blood pressure in diabetic patients inadequately controlled with combination antihypertensive regimen. Circulation. 2013;128(22).
Meeting abstract

Wei J, Tang Q, Liu L, et al. Combination of peroxisome proliferator-activated receptor alpha/gamma agonists may benefit type 2 diabetes patients with coronary artery disease through inhibition of inflammatory cytokine secretion. Exp Ther Med. 2013 Mar;5(3):783-8. PMID: 23408783.
No drug comparison of interest; Background medications

Wei L, MacDonald TM, Mackenzie IS. Pioglitazone and bladder cancer: a propensity score matched cohort study. Br J Clin Pharmacol. 2013 Jan;75(1):254-9. PMID: 22574756.
No drug comparison of interest

Weinstock RS, Umpierrez GE, Guerci B, et al. Safety and efficacy of dulaglutide vs. sitagliptin after 104 weeks in type 2 diabetes (AWARD-5). Diabetes. 2013;62((Weinstock R.S.; Umpierrez G.E.; Guerci B.; Nauck M.A.; Boleyn K.L.; Skrivanek Z.; Milicevic Z.) Syracuse, NY, Atlanta, GA, Nancy, France, Bad Lauterberg, Germany, Indianapolis, IN, Vienna, Austria):A258.
Meeting abstract

Weir DL, McAlister FA, Senthilselvan A, et al. Sitagliptin Use in Patients With Diabetes and Heart Failure: A Population-Based Retrospective Cohort Study. JACC Heart Fail. 2014 Jun 25PMID: 24998080.
Background medications

Weir DL, McAlister FA, Senthilselvan A, et al. The comparative safety and effectiveness of sitagliptin in patients with type 2 diabetes and heart failure. Diabetologia. 2013;56((Weir D.L.; McAlister F.A.; Senthilselvan A.; Dyck J.R.; Sandhu-Minhas J.K.; Eurich D.T.) University of Alberta, Edmonton, Canada):S392-S3.
Meeting abstract

Weir DL, McAlister FA, Senthilselvan S, et al. The comparative safety and effectiveness of sitagliptin in patients with type 2 diabetes and heart failure. Pharmacoepidemiology and Drug Safety. 2013;22((Weir D.L.; Senthilselvan S.; Eurich D.T.) Public Health Sciences, University of Alberta, Edmonton, Canada):131.
Meeting abstract

Weir DL, Senthilselva A, Dyck JR, et al. Comparative safety and effectiveness of sitagliptin in patients with type 2 diabetes and heart failure. Diabetes. 2013;62((Weir D.L.; Senthilselva A.; Dyck J.R.; Sandhuminhas J.K.; Mcalister F.A.; Eurich D.T.) Edmonton, Canada):A372.
Meeting abstract

Weir M, Januszewicz A, Gilbert R, et al. Effects of canagliflozin on blood pressure and adverse events related to osmotic diuresis and reduced intravascular volume in subjects with type 2 diabetes mellitus. Diabetologia. 2013;56((Weir M.) University of Maryland Medical Center, Baltimore, United States):S378.
Meeting abstract

Weir MR, Januszewicz A, Gilbert R, et al. Lower blood pressure (BP) with canagliflozin (CANA) in subjects with type 2 diabetes mellitus (T2DM). Diabetes. 2013;62((Weir M.R.; Januszewicz A.; Gilbert R.; Gonzalez F.L.; Meininger G.) Baltimore, MD, Warsaw, Poland, Toronto, ON, Canada, Monterrey, Mexico, Raritan, NJ):A278.
Meeting abstract

Weir MR, Kline I, Xie J, et al. Effect of canagliflozin on serum electrolytes in patients with type 2 diabetes in relation to estimated glomerular filtration rate (eGFR). Curr Med Res Opin. 2014 May 22:1-10. PMID: 24786834.
Handsearch

Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. Diabetologia. 2014 Dec;57(12):2475-84. PMID: 25208756.
Background medications

Weissman PN, Stewart MW, Cirkel DT, et al. Harmony 4: 3 year efficacy of albiglutide (ALBI) vs insulin glargine (GLAR) in patients with type 2 diabetes mellitus. Diabetologia. 2014;57(1):S340.
Meeting abstract

Wendel CS, Fotieo GG, Shah JH, et al. Incidence of non-severe hypoglycaemia and intensity of treatment among veterans with Type 2 diabetes in the USA: a prospective observational study. Diabet Med. 2014 Jun 30PMID: 24975871.
No drug comparison of interest

Wenten M, Gaebler JA, Hussein M, et al. Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medication: a follow-up study. Diabet Med. 2012 Nov;29(11):1412-8. PMID: 22416857.
No drug comparison of interest

Wenying Y, Chen L, Ji Q, et al. Efficacy and safety of liraglutide compared with glimepiride, both combined with metformin, in an Asian population. Diabetologia. 2010;53((Wenying Y.) China-Japan Friendship Hospital, Beijing, China):S330.
Meeting abstract

Wertz DA, Chang CL, Sarawate CA, et al. Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed-care population. Circulation: Cardiovascular Quality and Outcomes. 2010;3(5):538-45.
Background medications

White JR, Bastien A, Parikh S, et al. Dapagliflozin monotherapy and combination therapy reduces hyperglycemia in patients with type 2 diabetes. Pharmacotherapy. 2011;31(10):337e.
Meeting abstract

White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013 Oct 3;369(14):1327-35. PMID: 23992602.
Background medications; Comorbidity

White WB, Kupfer S, Nissen S, et al. Cardiovascular mortality in patients with type 2 diabetes and recent acute coronary syndromes from the examine trial. Journal of the American College of Cardiology. 2014;63(12):A116.
Meeting abstract

Wilding J, Blonde L, Chiasson JL, et al. Canagliflozin lowers HbA1c and blood pressure through weight lossindependent and weight loss-associated mechanisms. Diabetologia. 2013;56((Wilding J.) Department of Obesity and Endocrinology, University of Liverpool, United Kingdom):S379.
Meeting abstract

Wilding JP, Blonde L, Leiter LA, et al. Efficacy and safety of canagliflozin by baseline HbA and known duration of type 2 diabetes mellitus. J Diabetes Complications. 2014 Dec 31PMID: 25660137.
Comparison of two separate doses; Pooled data; Placebo-controlled trial

Wilding JP, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. Int J Clin Pract. 2013 Dec;67(12):1267-82. PMID: 24118688.
No drug comparison of interest

Wilding JP, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Ann Intern Med. 2012 Mar 20;156(6):405-15. PMID: 22431673.
No drug comparison of interest; Background medications

Wilding JPH, Blonde L, Leiter LA, et al. Efficacy and safety of canagliflozin by baseline HbA1c and known duration of type 2 diabetes mellitus. Journal of Diabetes and its Complications. 2015((Wilding J.P.H., J.P.H.Wilding@liverpool.ac.uk) Department of Obesity and Endocrinology, University of Liverpool, Liverpool, United Kingdom).
Background medications

Wilding JPH, Woo V, Pahor A, et al. Effect of dapagliflozin, a novel insulin-independent treatment, over 48 weeks in patients with type 2 diabetes poorly controlled with insulin. Diabetologia. 2010;53((Wilding J.P.H.) Department of Medicine, University of Liverpool, United Kingdom):S348.
Meeting abstract

Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. Diabetes Care. 2010 Jan;33(1):156-61. PMID: 19846797.
No drug comparison of interest; Background medications

Wilke T, Mueller S, Groth A, et al. Treatment-dependent and treatment-independent risk factors associated with the risk of diabetes-related events: A retrospective analysis based on 229,042 patients with type 2 diabetes mellitus. Cardiovascular Diabetology. 2015;14(1).
No drug comparison of interest; Background medications

Willemen MJ, Mantel-Teeuwisse AK, Straus SM, et al. Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization VigiBase. Diabetes Care. 2011 Feb;34(2):369-74. PMID: 21270195.
Does not account for confounding

Williams-Herman D, Engel SS, Round E, et al. Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes. BMC Endocr Disord. 2010;10:7. PMID: 20412573.
No drug comparison of interest; Background medications

Williams-Herman D, Seck T, Golm G, et al. Improvement in glycaemic control and ss-cell function over 2 years with sitagliptin as monotherapy or add-on therapy to metformin in patients with type 2 diabetes. Canadian Journal of Diabetes. 2009;33(3):257.
Meeting abstract

Williams-Herman D, Xu L, Teng R, et al. Effect of initial combination therapy with sitagliptin and metformin on beta-cell function in patients with type 2 diabetes. Diabetes Obes Metab. 2012 Jan;14(1):67-76. PMID: 22050786.
Handsearch

Williams-Herman DE, Seck TL, Golm G, et al. Long-term efficacy with sitagliptin as monotherapy or add-on therapy to metformin: Improvement in glycemic control over 2 years in patients with type 2 diabetes. Diabetes. 2009;58((Williams-Herman D.E.; Seck T.L.; Golm G.; Wang H.; Johnson J.; Kaufman K.D.; Goldstein B.J.) Rahway, United States).
Meeting abstract

Wilson C, Fleck P. Effect of alogliptin in combination with pioglitazone on glycaemic control by baseline HbA1c. Diabetologia. 2012;55((Wilson C.; Fleck P.) Takeda Global Research and Development Center, Inc., Deerfield, United States):S348.
Meeting abstract

Wintle M, Bruce S, MacConell L, et al. Safety and tolerability of exenatide BID in patients with type 2 diabetes: Integrated analysis of 3854 patients from 11 comparator controlled clinical trials. Diabetologia. 2009;52(S1):S303.
Meeting abstract

Woerle HJ, Kadowaki T, Haneda M, et al. Safety and efficacy of empagliflozin monotherapy in a 52-week study in Japanese patients with type 2 diabetes mellitus. Diabetologia. 2013;56((Woerle H.J.; Rattunde H.; Broedl U.C.) Boehringer Ingelheim, Germany):S371-S2.
Meeting abstract

Woerle HJ, Neubacher D, Patel S, et al. Safety and efficacy of linagliptin and basal insulin combination therapy in elderly patients (age (greater-than or equal to)70 years) with type 2 diabetes (T2D). J Am Geriatr Soc. 2013;61((Woerle H.J.; Von Eynatten M.) Boehringer Ingelheim, Ingelheim, Germany):S31-S2.
Meeting abstract

Wolffenbuttel BHR, Klaff LJ, Bhushan R, et al. Initiating insulin therapy in elderly patients with Type 2 diabetes: Efficacy and safety of lispro mix 25 vs. basal insulin combined with oral glucose-lowering agents. Diabetic Medicine. 2009;26(11):1147-55.
Background medications; No drug comparison of interest

Woo V, Davies M, De Zeeuw D, et al. Canagliflozin is effective and generally well tolerated in subjects with type 2 diabetes mellitus and Stage 3 chronic kidney disease. Diabetologia. 2013;56((Woo V.) University of Manitoba, Winnipeg, Canada):S382.
Meeting abstract

Woo V, Langkilde AM, Sugg J, et al. Dapagliflozin, a novel antihyperglycemic agent that promotes urinary glucose excretion, reduces systolic blood pressure in patients with type 2 diabetes mellitus. Circulation. 2011;124(21).
Meeting abstract

Woo V, Leiter LA, Cefalu WT, et al. Blood pressure reduction with dapagliflozin in patients with type 2 diabetes and cardiovascular disease. Circulation. 2013;128(22).
Meeting abstract

Woo V, Wysham C, Mathieu C, et al. Canagliflozin (CANA) added on to dipeptidyl peptidase-4 inhibitors (DPP-4I) or glucagon-like peptide-1 (GLP-1) agonists with or without other antihyperglycemic agents (AHAS) in type 2 diabetes mellitus (T2DM). Canadian Journal of Diabetes. 2013;37((Woo V.; Wysham C.; Mathieu C.; Desai M.; Alba M.; Capuano G.; Meininger G.) Winnipeg, MB CAN; Spokane, WA USA; Leuvan, Belgium; Raritan, NJ USA):S38.
Meeting abstract

Wright A, Kempegowda P, Abernethy G, et al. GLP-1 analogues treatment was not associated with additional weight loss over intensive lifestyle intervention in severely obese patients with type 2 diabetes. Diabetes. 2014;63((Wright A.; Kempegowda P.; Abernethy G.; Sadiqi H.; Philips C.R.; Mclease J.; Golics R.; Maxwell E.; John R.; Shakher J.; Stevens M.J.; Bellary S.; Tahrani A.A.) Birmingham, United Kingdom):A523.
Meeting abstract

Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: results from a population-based case-control study.

Cancer Causes Control. 2009 Nov;20(9):1617-22. PMID: 19653109.
Background medications

Wu JD, Xu XH, Zhu J, et al. Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus. Diabetes Technol Ther. 2011 Feb;13(2):143-8. PMID: 21284481.
Background medications

Wu LC, Chang CH, Chunag LM, et al. Anti-diabetic therapies and cancer risk among type 2 diabetes patients in Taiwan-a nationwide nested case-control study. Pharmacoepidemiology and Drug Safety. 2011;20((Wu L.-C.; Chang C.-H.; Chunag L.-M.; Lai M.-S.) Institute of Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan):S290.
Meeting abstract

Wu S, Li X, Zhang H. Effects of metformin on endothelial function in type 2 diabetes. Exp Ther Med. 2014 May;7(5):1349-53. PMID: 24940437.
Background medications

Wu T, Ma J, Bound MJ, et al. Effects of sitagliptin on glycemia, incretin hormones, and antropyloroduodenal motility in response to intraduodenal glucose infusion in healthy lean and obese humans, and patients with type 2 diabetes treated with or without metformin. Diabetes. 2014 Mar 19PMID: 24647737.
Follow-up less than 3 months

Wu YT, Gau CS. The cardiovascular risk of sulfonylureas on newly diagnosed type ii diabetes mellitus patients. Drug Safety. 2009;32(10):945-6.
Meeting abstract

Wygant GD, Chalamandaris AG, Iloeje UH, et al. Dapagliflozin is more effective than glipizide in achieving the composite outcome of glycemic control, weight reduction, and lack of hypoglycemia. Diabetes. 2012;61((Wygant G.D.; Chalamandaris A.-G.; Iloeje U.H.; Salsali A.; Grandy S.; Sugg J.E.; Rohwedder K.; Parikh S.J.) Princeton, United States):A604.
Meeting abstract

Wysham C, Bergenstal R, Yan P, et al. DURATION-2: Exenatide once weekly demonstrated superior glycaemic control and weight reduction compared to sitagliptin or pioglitazone after 26 weeks of treatment. Diabetologia. 2009;52(S1):S290.
Meeting abstract

Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide versus placebo and exenatide in type 2 diabetes (award-1). Diabetes. 2013;62((Wysham C.; Blevins T.; Arakaki R.; Colon G.; Garcia P.; Atisso C.; Kuhstoss D.; Scism-Bacon J.; Lakshmanan M.) Spokane, WA, Austin, TX, Honolulu, HI, San Juan, Puerto Rico, Monterrey, Mexico, Indianapolis, IN):A16.
Meeting abstract

Wysham CH, Woo VC, Mathieu C, et al. Canagliflozin (CANA) added on to dipeptidyl peptidase-4 inhibitors (DPP-4i) or glucagon-like peptide-1 (GLP-1) agonists with or without other antihyperglycemic agents (AHAs) in type 2 diabetes mellitus (T2DM). Diabetes. 2013;62((Wysham C.H.; Woo V.C.; Mathieu C.; Desai M.; Alba M.; Capuano G.; Meininger G.) Spokane, WA, Winnipeg, MB, Canada, Leuven, Belgium, Raritan, NJ):A279.
Meeting abstract

Xing Y, Ye S, Hu Y, et al. Podocyte as a potential target of inflammation: role of pioglitazone hydrochloride in patients with

type 2 diabetes. Endocr Pract. 2012 Jul-Aug;18(4):493-8. PMID: 22441004.
No drug comparison of interest

Xu W, Bi Y, Sun Z, et al. Comparison of glycemic control and beta-cell function in newly diagnosed type 2 diabetes patients treated with exenatide, insulin or pioglitazone: A multicentre, randomized, parallel-group trial (confidence). Diabetes. 2014;63((Xu W.; Bi Y.; Sun Z.; Li J.; Guo L.; Yang T.; Wu G.; Shi L.; Feng Z.; Qiu L.; Li Q.; Guo X.; Luo Z.; Lu J.; Shan Z.; Yang W.; Ji Q.; Yan L.; Li H.; Yu X.; Li S.; Zhou Z.; Lv X.; Liang Z.; Lin S.; Zeng L.; Yan J.; Ji L.; Weng J.) Guangzhou, China, Nanjing, China, Beijing, China, Zhanjiang, China, Guizhou, China, Chongqing, China, Hohhot, China, Harbin, China, Nanning, China, Shenyang, China, Xi'an, China, Kunming, China, Wuhan, China, Qingyuan, China, Changsha, China, Shenzhen, China, Shantou, China):A86.
Meeting abstract

Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin (CANA) in subjects with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) over 52 weeks. Diabetes. 2013;62((Yale J.-F.; Bakris G.; Cariou B.; Iglesias J.N.; Wajs E.; Figueroa K.; Jiang J.; Usiskin K.; Meininger G.) Montreal, QC, Canada, Chicago, IL, Nantes, France, Ciudad Real, Spain, Beerse, Belgium, Raritan, NJ):A277-A8.
Meeting abstract

Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2013 May;15(5):463-73. PMID: 23464594.
Background medications

Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. Diabetes Obes Metab. 2014 Jun 25PMID: 24965700.
Background medications

Yale JF, Bakris G, Wajs E, et al. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, improves glycaemic control and is well tolerated in type 2 diabetes subjects with moderate renal impairment. Diabetologia. 2012;55((Yale J.-F.) Royal Victoria Hospital, McGill University, Montreal, Canada):S312.
Meeting abstract

Yale JF, Damci T, Kaiser M, et al. Initiation of once daily insulin detemir is not associated with weight gain in patients with type 2 diabetes mellitus: Results from an observational study. Diabetology and Metabolic Syndrome. 2013;5(1).
No drug comparison of interest; Background medications

Yamasaki Y, Katakami N, Furukado S, et al. Long-term effects of pioglitazone on carotid atherosclerosis in Japanese patients with type 2 diabetes without a recent history of macrovascular morbidity. J Atheroscler Thromb. 2010 Nov 27;17(11):1132-40. PMID: 20686324.
Background medications

Yang F, Reusch JEB, Rosenstock J, et al. The long-acting GLP-1-receptor agonist albiglutide improves glycaemic control in type 2 diabetes: Time-course analysis. Diabetologia. 2009;52(S1):S59-S60.
Meeting abstract

Yang F, Rosenstock J, Reusch J, et al. The long-acting GLP-1-receptor agonist albiglutide for the treatment of type 2 diabetes: A time course analysis of

gastrointestinal adverse events in patients receiving concomitant background metformin. Canadian Journal of Diabetes. 2009;33(3):292.
Meeting abstract

Yang H, Marynchenko M, Bron M, et al. Comparison of hypoglycaemia risk and cost between oral antidiabetic monotherapies in elderly patients with type 2 diabetes mellitus in a U.S. population. Diabetologia. 2011;54((Yang H.; Marynchenko M.; Wu E.; Yu A.P.) Analysis Group, Inc., Boston, United States):S265.
Meeting abstract

Yang J, Vallarino C, Bron M, et al. A comparison of all-cause mortality with pioglitazone and insulin in type 2 diabetes: an expanded analysis from a retrospective cohort study. Curr Med Res Opin. 2014 Jul 1:1-25. PMID: 24983744.
No drug comparison of interest; Background medications

Yang L, Lu JC, Ding CH, et al. Glycemic control in 374 outpatients with type 2 diabetes mellitus. Academic Journal of Second Military Medical University. 2013;34(2):177-83.
No drug comparison of interest

Yang L, Song MQ, Zhang QL, et al. Effect of piglitazone and metformin on retinol-binding protein-4 and adiponectin in patients with type 2 diabetes mellitus complicated with non-alcohol fatty acid liver diseases. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2014 Jun;36(3):309-12. PMID: 24997826.
Non-English language

Yang W, Guan Y, Shentu Y, et al. Sitagliptin added to ongoing metformin therapy in chinese patients with type 2 diabetes significantly enhances glycemic control. Diabetes. 2011;60((Yang W.; Guan Y.; Shentu Y.; Li Z.; Johnsonlevonas A.O.; Engel S.S.; Kaufman K.D.; Goldstein B.J.; Alba M.) Beijing, China):A306.
Meeting abstract

Yang X, So WY, Ma RC, et al. Low HDL cholesterol, metformin use, and cancer risk in type 2 diabetes: the Hong Kong Diabetes Registry. Diabetes Care. 2011 Feb;34(2):375-80. PMID: 20980414.
No drug comparison of interest

Yasunari E, Takeno K, Funayama H, et al. Efficacy of pioglitazone on glycemic control and carotid intima-media thickness in type 2 diabetes patients with inadequate insulin therapy. J Diabetes Investig. 2011 Jan 24;2(1):56-62. PMID: 24843462.
No drug comparison of interest; Background medications

Ye S, Zheng M, Hu Y, et al. Hydrochloride pioglitazone decreases urinary monocyte chemoattractant protein-1 excretion in type 2 diabetics. Diabetes Res Clin Pract. 2010 Jun;88(3):247-51. PMID: 20371128.
Background medications

Yee MS, Pavitt DV, Dhanjil S, et al. The effects of rosiglitazone on carotid ultrasound indices and glycaemia in subjects with a high cardiovascular risk and Type 2 diabetes. Diabetic Medicine. 2009;26((Yee M.S.; Pavitt D.V.; Dhanjil S.; Godsland I.F.; Richmond W.; Johnston D.G.) Metabolic Medicine Unit, Imperial College London, London, United Kingdom):47.
Meeting abstract

Yeh HT, Hsieh CF, Tsai YW, et al. Effects of thiazolidinediones on cardiovascular events in patients with type 2 diabetes mellitus after drug-eluting stent implantation: a retrospective cohort study using the national health insurance database

in Taiwan. Clin Ther. 2012 Apr;34(4):885-93. PMID: 22440193.
No drug comparison of interest

Yokoe H, Yuasa F, Sugiura T, et al. The effect of pioglitazone on arterial baroreflex sensitivity and sympathetic nerve activity in patients with type 2 diabetes mellitus after myocardial infarction. European Heart Journal. 2009;30((Yokoe H.; Yuasa F.; Iwasaka T.) Kansai Medical University, Osaka, Japan):337.
Meeting abstract

Yokoe H, Yuasa F, Yo M, et al. The effect of pioglitazone on sympathetic and baroreflex function in type two diabetes mellitus after myocardial infarction. Journal of the American College of Cardiology. 2009;53(10):A157.
Meeting abstract

Yokoe H, Yuasa F, Yuyama R, et al. Effect of pioglitazone on arterial baroreflex sensitivity and sympathetic nerve activity in patients with acute myocardial infarction and type 2 diabetes mellitus. J Cardiovasc Pharmacol. 2012 Jun;59(6):563-9. PMID: 22361751.
Comorbidity; No drug comparison of interest

Yokoi H, Nakamura M, Muramatsu T, et al. Impact of pioglitazone on cardiovascular events in patients with type-2 diabetes mellitus after drug-eluting stent implantation. Journal of the American College of Cardiology. 2013;62(18):B65.
Meeting abstract

Yoon K, Shockey G, Teng R, et al. Initial combination therapy with sitagliptin and pioglitazone improves glycaemic control and measures of beta cell function compared with pioglitazone alone in patients with type 2 diabetes. Diabetologia. 2009;52(S1):S294.
Meeting abstract

Yoshida M, Yamamoto N, Saeki A, et al. Exenatide therapy reduced intina-media thickness of carotid artery in patients with type 2 diabetes. Diabetologia. 2012;55((Yoshida M.; Yamamoto N.; Saeki A.; Sugino M.) Internal Medicine, Aino Hospital, Ibaraki City, Japan):S322-S3.
Meeting abstract

Yoshii H, Onuma T, Yamazaki T, et al. Effects of Pioglitazone on Macrovascular Events in Patients with Type 2 Diabetes Mellitus at High Risk of Stroke: The PROFIT-J Study. J Atheroscler Thromb. 2014 Jun 25;21(6):563-73. PMID: 24477028.
No drug comparison of interest; Backgroundmedications

You SH, Kim BS, Hong SJ, et al. The effects of pioglitazone in reducing atherosclerosis progression and neointima volume in type 2 diabetic patients: prospective randomized study with volumetric intravascular ultrasonography analysis. Korean Circ J. 2010 Dec;40(12):625-31. PMID: 21267384.
Placebo-controlled trial; Comorbidity

Young MA, Wald JA, Matthews JE, et al. Effect of renal impairment on the pharmacokinetics, efficacy, and safety of albiglutide. Postgrad Med. 2014 May;126(3):35-46. PMID: 24918790.
Follow-up less than 3 months

Yu OHY, Filion KB, Azoulay L, et al. Incretin-based drugs and the risk of congestive heart failure. Diabetes Care. 2015;38(2):277-84.
Does not account for confounding; Background medications

Yu S, Yang J, Bron M, et al. An assessment of all-cause mortality for pioglitazone compared with insulin in patients with type 2 diabetes mellitus. Diabetologia. 2012;55((Yu S.; Yang J.; Bron M.; Harikrishnan V.) Takeda Pharmaceuticals International, Inc, Deerfield, United States):S499.
Meeting abstract

Zannad F, Cannon C, Cushman W, et al. Alogliptin in patients with type 2 diabetes after acute coronary syndromes: Heart failure outcomes and cardiovascular safety in heart failure patients. Journal of the American College of Cardiology. 2014;63(12):A117.
Meeting abstract

Zavattaro M, Caputo M, Sama MT, et al. One-year treatment with liraglutide improved renal function in patients with type 2 diabetes: a pilot prospective study. Endocrine. 2015 Jan 9PMID: 25572181.
Background medications; No drug comparison of interest

Zeng Z, Choi DS, Mohan V, et al. Efficacy and safety of linagliptin as monotherapy or add-on treatment in Asian patients with suboptimal glycemic control: a pooled analysis. Curr Med Res Opin. 2015 Jan;31(1):99-106. PMID: 25215428.
Background medications; No drug comparison of interest

Zeng Z, Choi DS, Mohan V, et al. Linagliptin is efficacious and well tolerated in asian patients with inadequately controlled type 2 diabetes. Diabetes. 2012;61((Zeng Z.; Choi D.S.; Mohan V.; Emser A.; Siddiqui K.; Gong Y.; Patel S.; Woerle H.-J.) Beijing, China):A300.
Meeting abstract

Zeng Z, Yang JK, Tong N, et al. Efficacy and safety of linagliptin added to metformin and sulphonylurea in Chinese patients with type 2 diabetes: A sub-analysis of data from a randomised clinical trial. Curr Med Res Opin. 2013;29(8):921-9.
No drug comparison of interest

Zhang DD, Liu F, Jia W. Metformin reduces serum CA199 levels in type 2 diabetic patients with time-effect and gender difference. Diabetologia. 2013;56((Zhang D.D.; Liu F.; Jia W.) Dept of Endocrinology and Metabolism, Shanghai Jiaotong University, Affiliated Sixth People's Hospital, Shanghai, China):S387.
Meeting abstract

Zhang L, Feng Y, List J, et al. Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus: effects on glycaemic control and body weight. Diabetes Obes Metab; 2010. p. 510-6.
No drug comparison of interest; Placebo-controlled trial

Zhang SL, Chen ZC, Yan L, et al. Determinants for inadequate glycaemic control in Chinese patients with mild-to-moderate type 2 diabetes on oral antidiabetic drugs alone. Chinese Medical Journal. 2011;124(16):2461-8.
Background medications

Zhang X, Mettler T, Harmsen WS, et al. Continuation of metformin use after a diagnosis of cirrhosis significantly improved survival of patients with type II diabetes (DM). Hepatology. 2013;58(4):331A.
Meeting abstract

Zhang XQ, Zhu S, Chen LC, et al. Risk of cardiovascular diaseases associated with antidiabetic monotherapy intervals in type-2 diabetic patients-a preliminiary study on

taiwan pay-for-performance diabetes registry. Value in Health. 2013;16(3):A158.
Meeting abstract

Zhang XY, Du JL, Jia YJ, et al. [Primary preventive effect of metformin upon atherosclerosis in patients with type 2 diabetes mellitus]. Zhonghua Yi Xue Za Zhi. 2009 Aug 11;89(30):2134-7. PMID: 20058619.
Background medications

Zhao M, Shao JQ, Du H. Effects of three antidiabetics on insulin and leptin in Chinese type 2 diabetes. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 2010;4(2):65-8.
No outcome of interest

Zhao Z, Spanheimer R, Perez A. Effect of pioglitazone and metformin fixed-dose combination on glycaemic control in untreated patients. Diabetologia. 2009;52(S1):S335.
Meeting abstract

Zheng JY, Tang YH, Zou JJ. Extended-release metformin in treatment of patients with type 2 diabetes: Efficacy and safety. Academic Journal of Second Military Medical University. 2009;30(1):101-3.
Meeting abstract

Zilov A, Naggar NE, Shah S, et al. Insulin detemir in the management of type 2 diabetes in non-Western countries: Safety and effectiveness data from the A1chieve observational study. Diabetes Research and Clinical Practice. 2013;101(3):317-25.
No drug comparison of interest

Zinman B, Gough S, Pratley R, et al. Achieving glycaemic control and weight loss with incretin-based therapies: A comparison of liraglutide, exenatide, and sitagliptin. Diabetologia. 2011;54((Zinman B.) Mt Sinai Hospital, Toronto, Canada):S324.
Meeting abstract

Zinman B, Haffner SM, Herman WH, et al. Effect of rosiglitazone, metformin, and glyburide on bone biomarkers in patients with type 2 diabetes. J Clin Endocrinol Metab. 2010 Jan;95(1):134-42. PMID: 19875477.
No outcome of interest

Zinman B, Harris SB, Neuman J, et al. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE Trial): A double-blind randomized controlled study. Obstetrical and Gynecological Survey. 2010;65(12):771-2.
No original data; Abstract only

Zinman B, Inzucchi SE, Lachin J, et al. Design of the empagliflozin cardiovascular (CV) outcome event trial in type 2 diabetes (T2D). Canadian Journal of Diabetes. 2013;37((Zinman B.; Inzucchi S.E.; Lachin J.; Wanner C.; Ferrari R.; Bluhmki E.; Hantel S.; Johansen O.E.; Woerle H.-J.; Broedl U.C.) Toronto, ON CAN; New Haven, CT USA; Washington, DC USA; Wurzburg, Germany; Ingelheim, Germany; Biberach, Germany):S29-S30.
Meeting abstract

Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). Cardiovasc Diabetol. 2014;13:102. PMID: 24943000.
Protocol; No original data

Zinman B, Schmidt WE, Moses A, et al. Achieving a clinically relevant composite outcome of an HbA1c of <7% without

weight gain or hypoglycaemia in type 2 diabetes: a meta-analysis of the liraglutide clinical trial programme. Diabetes Obes Metab. 2012 Jan;14(1):77-82. PMID: 21883806.
Does not meet study design criteria; Background medications

Ziyadeh N, McAfee AT, Koro C, et al. The thiazolidinediones rosiglitazone and pioglitazone and the risk of coronary heart disease: a retrospective cohort study using a US health insurance database. Clin Ther. 2009 Nov;31(11):2665-77. PMID: 20110009.
Background medications

Appendix D. Evidence Tables

Table D1. Characteristics of studies evaluating diabetes medications in terms of intermediate outcomes

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Aaboe, 2010[1] Denmark NCT00838903	2007 2008 12 Wks	No	Not Extracted	Yes	NR/ 24 Outpatient clinic not specified and in response to local advertisement	HbA1c >10% or <7%, on metformin monotherapy for less than 3 months, taking additional medication that affect glucose control, history of GI surgery, positive measurements of islet cell auto-antibodies (ICA) and/ or glutamate decarboxylase-65 (GAD-65) auto-antibodies, elevated liver enzymes (ALAT or ASAT) twice the respective upper normal value, elevated serum creatinine concentration (>130µmol/L), severe CVD (NYHA group III or IV), Albuminuria
Ahren, 2014[2] Country NR NCT01126580	2009 2013 104 Wks	Yes	Not Extracted	Yes	NR/ 1049 NR	Age <18 yrs, HbA1c > 10.00% or <7.00%, BMI <20 or >45 kg/m2, any liver disease, any kidney disease, adequate glycemic control while taking background metformin (>=1500mg or maximum tolerated dose) >=3 months before screening, abnormal thyroid-stimulating hormone concentration and not clinically euthyroid, ongoing symptomatic biliary disease, history of pancreatitis, recent clinically significant cardiovascular and/or cerebrovascular disease (<=2 months before screening), treated gastroparesis, history of GI surgery thought to significantly affect upper GI function, history of most cancers not in remission for at least 3 yrs, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, resting SBP >160mmHg and/or DBP>100mmHg,
Alba, 2013[3] Multi-continent NCT00734474	Neither year reported 12 Wks	Yes	Not Extracted	Yes	NR/ 211 NR	Age <30 or >65 yrs, HbA1c >10% or < 7% if drug naive, HbA1c >9% or <6.5% if on antihyperglycaemic agent monotherapy or low-dose combination therapy, duration of type 2 DM >5 yrs, any liver disease, any kidney disease, history of CVD, current use of sitagliptin, vildagliptin, exenatide, PPARr agonist within the prior 12 wks fasting fingerstick glucose <7.2mmol/l or 14.4mmol/l at week 12

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Apovian, 2010[4] US No	2006 -2008 24 Wks	No	Not Extracted	No	NR/ 194 NR	Age <18 and >75 yrs, HbA1c >10% or < 6.6%, BMI <25 and >39.9kg/m2 lacking history of stable body weight(varying by >5% in last 6 months), not treated for at least 6 wks with a stable dose of metformin or a sulfonylurea, use of exogenous insulin, alpha-glucosidase inhibitors, a thiazolidinedione, use of weight loss agents within 6 months before study entry, evidence of poorly controlled hypertension within the previous 3 months, history or presence of cardiac disease within 3 yrs of screening
Arechavaleta, 2011[5] Multi-national NCT01023581	Neither year reported 30 Wks	Yes	Not Extracted	Yes	NR/ 1035 NR	Age <18 yrs, HbA1c >9% or <6.50%, not on a stable dose of metformin (>1500 mg/day) as well as diet and exercise for past 12 wks, history of type 1 diabetes, used any Anti Hypoglycemic Agent besides metformin within 12 wks of the screening visit, renal function impairment prohibiting the use of metformin, fasting fingerstick glucose of <6.1 or >13.3 mmol/l at randomization, stable medications for hypertension, thyroid disease, Hormone replacement therapy, oral contraceptive pills
Arjona Ferreira, 2013[6] Multinational NCT00915772	Neither year reported 58 Wks	Yes	Not Extracted	Yes	NR/ 426 NR	Age <30yrs, HbA1c > 9.00% or <7.00%, prior or current use of insulin, any liver disease, did NOT have moderate to severe chronic renal insufficiency (eGFR>=50 ml/min/1.73m2 using the Modification of Diet in Renal Disease equation), on dialysis or likely to require dialysis for the duration of the study, acute renal disease, history of renal transplant, history of ketoacidosis, recent (within 3 months) cardiovascular event, thyroid stimulating hormone outside the reference range, triglycerides>600mg/dl, at visit 2 FPG>260mg/dl and unlikely to improve with diet/exercise, at visit 3, FPG>250mg/dl consistently (i.e., measurement repeated and confirmed within 7 days), at visit 4 FPG>240mg/dl consistently, at visit5, finger-stick glucose > 240 or <120mg/dl
Aschner, 2010[7] Multi-continent Not extracted	Neither year reported 24 wks	Run-in period but number excluded was NR	NR	Yes	2068/1050 NR	Age <18 or >78 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >9%, treatment naive, no Type 2 DM, FPG <120 or >250 mg/dL, triglycerides >600 mg/dL, creatine kinase (CK) > 2x upper limit normal

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Aschner, 2012[8] Multi-continent NCT01106677	2008 -2011 24 Wks	No	Not Extracted	Yes	NR/ 515 NR	Age <35 or >70 yrs, HbA1c >=11% or <7, BMI <25 or >45 kg/m^2, duration of type 2 DM <6 months, any liver disease, any kidney disease, FPG >14.4 mmol/L, treated with oral anti-diabetic drugs other than metformin in past 3 months, received SU+MET In past year, prior use of GLP-1 or DPP-4, any disorder that the investigator felt woudld compromise the patient's safety, unwilling to self-monitor blood glucose (BG) or keep diary
Bailey, 2005[9] UK, 14 European countries Not extracted	Not extracted 24 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 or >70 yrs, history of CVD, no Type 2 DM, other
Bailey, 2013[10] Multi-continent NCT00968812	2007- 2008 102 Wks	Yes	Not Extracted	Yes	NR/ 546 NR	Age <18 or >77 yrs, HbA1c > 10% or < 7%, BMI >45 kg/m^2, any liver disease, any kidney disease, history of CVD, C-peptide concentration <0.34 nmol/L, not taking stable dose of metformin for at least 8 wks prior to enrollment, creatine kinase more than 3 times upper limit of normal, symptoms of poorly controlled diabetes, SBP >=180 mmHg, DBP >=110 mmHg, clinically significant haematological, oncological, endocrine, psychiatric, or rheumatic disease, NYHA class III or IV congestive heart failure
Bakris, 2003[11] US and UK Not extracted	Not extracted 52 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	NR
Bakris, 2006[12] US, Multi-continent, South America, Europe Not extracted	Neither year reported 32 Wks	Yes	< 6 months	Yes	560/514 NR	Age <40 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI <22 kg/m^2, use of any TZD in the 3 months prior to screening, use of insulin for ≥ 6 months at any time prior to screening, anemia, severe angina, SBP >159 mm Hg (can't adjust the BP meds during the trial), DBP >99 mm Hg

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Barnett, 2012[13] Multi-continent NCT00707993	2008- 2010 52 Wks	Yes	Not Extracted	Yes	227 NR	Age <18 or >80 yrs, HbA1c >10.0% (9.0% for Canada) or <7.0% for treatment naïve patients, HbA1c > 9.0% or <6.5% for patients receiving an oral anti-diabetes drug, BMI >40kg/m^2, Prior or current use of insulin, any liver disease, any kidney disease, contraindication or history of intolerance to metformin, pregnant, nursing, not using adequate contraception, MI, stoke, or TIA in last 6 months, changed glucose-lowing treatment <10 wks prior to informed consent, hereditary galactose intolerance, treatment with GLP-1 analogue, TZD, or an anti-obesity drug within the previous 3 months, or any investigational agent within the previous 2 months, hypersensitivity or allergy to the investigational drugs
Bergenstal, 2010[14] Multi-continent NCT00528879	2008- 2008 26 Wks	No	Not Extracted	Yes	NR/ 514 Outpatient: primary care	Age <18yrs, HbA1c > 11% or < 7.10%, BMI <25 or >45kg/m^2, prior or current use of insulin, prior or current use of study drug, pregnant, nursing, not using adequate contraception, not treated with a stable metformin regimen for at least 2 months before screening, no type 2 DM, FPG >/= 280 mg/dL (15.5 mmol/L), clinically significant laboratory test values, physical examination, or electrocardiogram results, clinically significant medical condition (e.g., hepatic disease, renal disease, cardiovascular disease, gastroparesis, malignant disease, macular edema, chronic infections), drug or alcohol abuse, donated blood within 60 days of screening or planning to donate blood during study, major surgery or blood transfusion within 2 months of screening, current treatment with alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide, systemic corticosteroids or intrapulmonary steroids, drugs interacting with the CYP2C8 enzyme system, or any investigational drug, known allergies or hypersensitivity to any component of study treatment, or previously experienced a clinically significant adverse event related to TZD or DPP-4 inhibitor use
Bergenstal, 2012[15] Multi-continent NCT00740051	2008 - 2011 156 Wks	No	Not Extracted	Yes	NR/ 666 clinical sites unspecified	Age <18 or >75yrs, HbA1c > 10% or <7%, BMI <25kg/m^2 (<23 kg/m^2 for Asians) or >45kg/m^2, prior or current use of insulin, history of CVD, neuropathy, retinopathy, NOT receiving metformin (stable dose >/=1,500 mg/day or maximally tolerated dose for >/=12 wks before screening), diabetic nephropathy, GI disease, previous bariatric surgery, pancreatitis, previous exposure to other oral anti-hyperglycemic or weight-lowering drugs within 12 wks, >1 week of insulin within 6 months, or another GLP-1 mimetic or analog at any time.

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Blonde, 2002[16] US Not extracted	Not extracted 16 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <30 or >75 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <7.4%, no Type 2 DM, other
Bolinder, 2012[17] Europe NCT00622284	2009 2011 102 Wks	Yes	Not Extracted	Yes	NR/ 182 NR	Age <55 or >75 yrs (women), <30 or >75 yrs (men), HbA1c > 8.50% or <6.50%, BMI <25kg/m^2 and body weight >120 kg, prior or current use of insulin, any liver disease, any kidney disease, pregnant, nursing, FPG >240 mg/dl (>13.2 mmol/l), diabetes treatment includes other drugs besides metformin, metformin treatment <1500 mg/d, not on stable metformin treatment at least 12 wks before enrollment perimenopausal women, body weight change >5% within 3 months serum total bilirubin >34 µmol/L; hemoglobin <105 g/L (10.5 g/dL) for men and <95 g/L (9.5 g/dL) for women; abnormal thyroid stimulating hormone level; 25-hydroxyvitamin D level <12 ng/mL (<30 nmol/L), history of osteoporotic fracture, bilateral hip replacement, spinal deformity or spinal surgery, metabolic bone disease or disease known to significantly influence bone metabolism or use of medication known to significantly influence bone metabolism within 6 months of enrolment, T-score less than 2.0 for bone mineral density at lumbar spine, femoral neck, or total hip at baseline DXA measurement, SBP >/=180 mmHg and/or DBP >/=110 mmHg; cardiovascular event within 6 months of enrolment; congestive heart failure; significant respiratory, hematological, oncological, endocrine, immunological (including hypersensitivity to study medications); alcohol and/or substance misuse disorders; a history of bariatric surgery; use of weight loss medication within 30 days of enrollment
Borges, 2011[18] Multi-continent NCT01318109	2006 2008 80 Wks	No	Not Extracted	Yes	NR/ 688 NR	Age <18 or >75 yrs, HbA1c > 10.5% or <7.5%. BMI <= 25 kg/m^2, prior use of any diabetes treatment, fasting glucose <7 mmol/l

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Campbell, 1994[19] UK Not extracted	Not extracted 52 wks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <40 or >69 yrs, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other
Cefalu, 2013[20] Multi-continent NCT00643851	2009 2011 52 Wks	Yes	Not Extracted	Yes	NR/ 1452 NR	Age <18, >80 yrs, HbA1c < 7% or >9.5%, Any kidney disease, Not on stable metformin therapy (for at least 10 wks prior TZD use in 16 wks before screening, history of more than 1 severe hypoglycemic episode within 6 months, repeated measurements of fasting plasma glucose or fasting self-monitored blood glucose, or both, of 15.0 mmol/L or more during the pretreatment phase;
Charbonnel, 2006[21] Multi-continent Not extracted	Neither year reported 24 Wks	Run-in period but number excluded was NR	NR	Yes	1464/701 NR	Age <18 or >78 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >10%, Type 1 DM, insulin use within 8 wks of screening, FPG >14.4mmol/l
Charpentier, 2001[22] France Not extracted	Not extracted 20 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age ≤34 or ≥71 yrs, any kidney disease, history of CVD, no Type 2 DM, other
Chawla, 2013[23] India NCT00798161	2008 2009 16 Wks	No	Not Extracted	No	NR/ 52 NR	Age <18 yrs, HbA1c < 7.5% or >11%, Any liver disease ,Any kidney disease, History of CVD, not on metformin monotherapy of >=1500mg/day for at least 1 month, FPG<140mg/dl or >270 mg/dl

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Chien, 2007[24] Taiwan Not extracted	Neither year reported 16 Wks	No run-in period	< 6 months	Yes	166/100 5 medical centers. Does not specify inpatient or outpatient	Age <30 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, retinopathy, HbA1c > 12% and FPG>250 mg/dL at screening visit, HbA1c < 7% and FPG<140 mg/dL at screening visit, BMI <18.5 kg/m^2 or >35 kg/m2, current significant GI disorder, hyperglycemic hyperosmolar non-ketotic coma, hypersensitivity to glyburide or metformin, current infection, treatment with insulin in last 6 months, surgery in past 4 wks, history of cancer in 5 yrs, on concurrent drugs affect sugar metabolism, FPG < 140 mg/dl at second visit, not on a stable dose of SU at baseline or dose of metformin>1000mg/day or SU dose too low (glyburide or gliclazide<10 mg/day, glimepiride<4mg/d, gliclazide<160mg/d)
Comaschi, 2007[25] Italy Not extracted	Neither year reported 6 Months	Run-in period but number excluded was NR	< 6 months	Yes	398/250 NR	Age <35 yrs, HbA1c < 7.5% or >11%, had not received SU or metformin as a monotherapy at a stable dose for at least 3months, fasting C-peptide <0.33 nmol/L
Davies, 2007[26] United Kingdom Not extracted	Neither year reported 4 months	Run-in period but number excluded was NR	< 6 months	NR	NR/82 NR	Age <30 or >80 yrs, history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c >7.0%, BMI >43 kg/m^2, not using adequate contraception, history of previous insulin use for >2 wks, duration of Type 2 DM <12 months, c-peptide levels <0.33, severe concurrent disease, serum Cr >150umol/l
DeFronzo, 1995[27] US Not extracted	Not extracted 29 wks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <40 or >70 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
DeFronzo, 2005[28] US NR	2002 2003 30 wks	Yes	Not extracted	Yes	NR/336 NR	Fasting glucose >13.3 mmol/l. Not on metformin >=1500mg/day for at least 3 months before screening. If weight not stable (=/-10%) for 3 months before screening. Female subjects were not postmenopausal, surgically sterile, or using contraceptives for 3 months before screening and continuing throughout the study. Use of sulfonylureas, meglitinides, thiazolidinediones,-glucosidase inhibitors, exogenous insulin therapy, weight loss drugs, corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug, or e.
DeFronzo, 2009[29] NR	Neither year reported 24 wks	Yes	< 6 months	Yes	1462/743 NR	Age <18 or >77 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), contraindication or history of intolerance to metformin, neuropathy, retinopathy, HbA1c < 7% or >10%, BMI >40 kg/m^2, pregnant, nursing, alcohol or drug abuse, NYHA III and IV, LVEF <40%
DeFronzo, 2010[30] US Not extracted	Start Year 2006 End Year 2008 20 wks	No run-in period	< 6 months	Yes	NR/137 NR	Age <18 or >75 yrs, HbA1c <6.8% or >10%, BMI <25 kg/m^2 or >40 kg/m^2, not on stable dose of metformin for at least 6 wks, body weight stable for past 6 months, islet cell auto-antibodies, treatment with any other ODM (other than metformin)
DeFronzo, 2012[31] Multi-continent NCT00855166	Neither year reported 26 Wks	Yes	Not Extracted	Yes	NR/ 1554 NR	Age <18 or >80 yrs, HbA1c > 10% before and after run-in/stabilization period or <7.5% before and after run-in/stabilization period, BMI <23 or >45kg/m2, Any liver disease, Any kidney disease, Retinopathy, Not using adequate contraception, fasting C-peptide <0.26nmol/l, not on met monotherapy (stable met dose >1500mg/d for >=2 months), SBP/DBP>160/100mmHg, hemoglobin < 12g/dl for men, <10g/dl for women, class 3 or 4 CHF, cardiac surgery or acute MI within last 6 months, TSH > ULN, treated diabetic gastroparesis, no willingness or ability to perform self-monitoring of blood glucose or to provide written informed consent, FPG>16.7mmol/l after run-in/stabilization period, oral or systemically injected glucocorticoids or weight-loss drugs within 3 months of randomization

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Del Prato, 2015[32] Multi-continent NCT00660907	Neither year reported 208 wks	No	Not extracted	Yes	NR/814 NR	Reference to other studies.
Del Prato, 2014[33] Mutli-continent NCT00856284	Neither year reported 104 wks	Yes	Not extracted	Yes	NR/2639 NR	Systolic blood pressure >150mm hg. Diastolic blood pressure >90 mm hg. History of cancer. Prior use of any other diabetes drug for the last 2 months.
Derosa, 2004[34] Italy Not extracted	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <46 or >67 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Derosa, 2005[35] Italy Not extracted	Neither year reported 12 Months	No run-in period	< 6 months	NR	NR/99 case-report forms or computerized clinic registers	Age ≤18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), poorly controlled on prior treatments (e.g., failed initial treatment), neuropathy, retinopathy, HbA1c <7.5%, BMI ≤25.3 kg/m^2, pregnant, nursing, not using adequate contraception, if no Type 2 DM for minimum 6 months based on ADA criteria, if no metabolic syndrome based on NCEP ATP III, if no hypertension, triglycerides ≤150mg/dl, C-peptide ≤1.0ng/ml, history of ketoacidosis, anemia, receiving lipid-lowering meds, anticoagulation, glimepiride, or a TZD

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Derosa, 2005[36] Italy Not extracted	Neither year reported 12 Months	No run-in period	< 6 months	NR	NR/99 case notes and/or clinic registers	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), neuropathy, retinopathy, HbA1c < 7%, pregnant, nursing, not using adequate contraception, no type 2 DM by ADA criteria for at least 6 mo, fasting c-peptide <1.0ng/ml, no metabolic syndrome with at least 3 components (based on NCEP ATP III), ketoacidosis, anemia, cerebrovascular conditions within 6 months, consumption of glimepiride or TZDs or prior intolerance to these medications
Derosa, 2005[37] Italy Not extracted	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <18 yrs, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <7.5%, no Type 2 DM, other
Derosa, 2009[38] Italy Not extracted	Neither year reported 15 Months	Fewer than 10% of participants were excluded during run-in	< 6 months	NR	271/252 Outpatient primary care, computerized clinic registry	Age <18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c <6.5%, BMI <25 kg/m^2 or >30 kg/m^2, pregnant, nursing, not using adequate contraception, no Type 2 DM, history of ketoacidosis, severe anemia
Derosa, 2010[39] Italy Not extracted	Neither year reported 12 months	No run-in period	< 6 months	No	128/128 patients identified from case notes and clinical registers	Age <18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c < 8%, BMI <25 kg/m^2 or ≥30 kg/m^2, pregnant, nursing, not using adequate contraception, history of ketoacidosis, severe anemia, not intolerant to metformin at maximum dosage (3,000 mg/day), not on metformin, diabetic neuropathy

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Derosa, 2011[40] Italy NCT00660907	Neither year reported 12 Months	No	Not Extracted	No	NR/ 111 Inpatient/hospital Outpatient: primary care	Age < 18 yrs, HbA1c <=8%, BMI <25 or >=30 kg/m2, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, not taking 1000-2000 mg/d of metformin, history of ketoacidosis, history of cerebrovascular condition, severe anemia, serious CVD (eg, NYHA classes II-IV CHF or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment also were excluded, not intolerant of metformin 2500-3000 mg/d
Derosa, 2012[41] Italy NCT00601250	Neither year reported 12 Months	Yes	Not Extracted	No	NR/ 178 outpatient clinic within a hospital but not further specified	Age <=18yrs ,HbA1c <=8%, BMI <25 and >= 33kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, history of ketoacidosis, severe anemia, Patients with serious cardiovascular disease (CVD) (e.g., NYHA class I-IV CHF or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months
Derosa, 2013[42] Italy NCT00309608	2008 2010 12 Months	Yes	Not Extracted	NR	NR/ 178 NR	Age <=18 yrs, HbA1c <=7.5%, BMI <25 or >=31 kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, ketoacidosis, severe anemia, NYHA 1-4 congestive heart failure
Derosa, 2013[43] Italy NCT00395512	2008 2010 12 Months	Yes	Not Extracted	No	NR/ 171 NR	Age <=18 yrs, HbA1c <=7.5%, BMI<25 or >=34.9kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, history of ketoacidosis, acute or chronic pancreatitis, severe anemia, serous CVD (e.g. NYHA class 1-4 CHF, MI, stroke) or cerebrovascular conditions within 6 months before study enrollment, taking gygtemic glucocorticoids, taking weight reducing drugs such as sibutramine or orlistat, or any medications that miht preclude safe participation in the study

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Diamant, 2010[44] Multi-continent NCT00286442	2008 2009 26 Wks	Yes	Not Extracted	Yes	NR/ 321 NR	Age 18 yrs or older, HbA1c >11% or <7.1%, BMI <25kg/m2 and >45kg/m2, Unstable body weight within 3 months, more than three episodes of major hypoglycaemia within 6 months of screening, treatment within 4 wks of screening with systemic glucocorticoids, treatment for longer than 2 wks with insulin, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, exenatide twice-aday formulation, dipeptidyl peptidase-4 inhibitors, or pramlintide acetate within 3 months of screening, not treated with a stable dose of metformin of 1500 mg or more per day for at least 8 wks prior to screening
Einhorn, 2000[45] US Not extracted	Not extracted 16 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <8.0%, no Type 2 DM, other
Erdem, 2008[46] Turkey Not extracted	Neither year reported 12 Wks	No run-in period	< 6 months	No	53/44 outpatient department of internal medicine clinic	Age <30 or >70 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI >35 kg/m^2, other chronic disease as detected by history and physical
Erem, 2014[47] Turkey NCT00263276	Neither year reported 52 Wks	Yes	Not Extracted	No	NR/ 60 NR	Age <30 or >70 yrs, HbA1c < 8% when FPG<126mg/dl, <7% if FBG is 126 - 139 mg/dl and HOMA-IR>3, not newly diagnosed, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, COPD, ketoacidosis or ketonuria, NYHAC Class 3/4 CHF, history of lactic acidosis, malignancy, thyroid disease, or chronic inflammatory diseases or rheumatic disease, substance abuse, steroid treatment, active infection

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Esposito, 2011[48] Italy NCT00749190	Neither year reported 24 Wks	No	Not Extracted	Yes	NR/ 110 investigators' practices	Age <30 and >75 yrs, HbA1c >10% or <7%, BMI </=25kg/m2 and unstable weight in last 6 months or evidence of participation in weight reduction programs, "Newly diagnosed", Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Pregnant, Nursing, any investigational drug in past 3 mo, use of agents affecting glycaemic control (such as systemic glucocorticoids and weight loss drugs), acute disease or infection, recent (within 3 months) cardiovascular events or surger, immunological disorders, any condition that might compromise adherence to the study, patients with positive antibodies to glutamate decarboxylase, participation in weight loss program or unstable wt in past 6 mo, patients with C-peptide levels less than 0.25 pmol/l (<0.76 ng/l)
Esteghamati, 2014[49] Iran NCT01177813	2011 2011 12 Wks	No	Not Extracted	No	NR/ 98 Outpatient: subspecialty care setting	not newly diagnosed with diabetes, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, current use of oral antihyperglycemic medication sofr treatment of diabetes or other hyperglycemia-associated conditions(e.g. polycystic ovary syndrome), taking corticosteroids, regularly consuming alcoholic beverages
Esteghamati, 2015[50] Iran NCT01963663	2012 2013 3 months	No	Not extracted	No	NR/84 NR	History of over-thecounter vitamin or anti-oxidant supplements. Significant chronic illnesses of the heart, kidney or lung.
Farcasiu, 2011[51] Multi-continent NCT01012037	2006 2009 16 Wks	Yes	Not Extracted	Yes	NR/ 302 NR	Age <30 - >75 yrs, HbA1c > 1.8 X ULN or <1.2 X ULN, BMI >40 kg/m2, Any liver disease, metformin <1500mg, on other oral dm med besides metofrmin, history of severe hypoglycemia within 6 months, CHF, renal transplantation, irregular sleep-wake cycle

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Feinglos, 2005[52] US Not extracted	Not extracted 16 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <30 or >81 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <7.0% or >8.5%, no Type 2 DM, other
Ferrannini, 2013[53] Multi-continent NCT01167881	 Neither year reported 90 Wks	Yes	Not Extracted	Yes	NR/ 659 NR	Age <18 or>79 yrs, HbA1c >=10% or <7%, BMI>40, successfully completed one of the two 12-wk dose-finding studies (refid 584 or 1334)
Fidan, 2011[54] Turkey (assumed based on affilations) NCT01340664	Neither year reported 12 Wks	Yes	Not Extracted	NR	NR/ 40 NR	Age <40 yrs, HbA1c >10% or <7%, Prior use of any diabetes treatment, Any kidney disease, Pregnant, Not using adequate contraception, malignancy, chronic inflammatory diseases, active infection, COPD, lacking combination of the following (HbA1c 8-<10 or FPG <=140) or (HbA1c 7-8 AND (FPG 120-140 or HOMA-IR >3)), class 3-4 coronary insufficiency, not completing uptitration run-in
Fonseca, 2000[55] US Not extracted	Not extracted 26 wks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Fonseca, 2012[56] US and Latin America NCT01159600	2009 2010 18 Wks	Yes	Not Extracted	Yes	NR/ 282 NR	Adults, HbA1c >11% or <7.5%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Not using adequate contraception, weight loss >10% in 3 mo before screening, unable to finish lead-in period (stabilitized on met 1500 mg/d), history of ketoacidosis, alcohol or drug abuse or unstable psychiatric disorder, hemoglobinopathy, blood/plasma donation in past 3 mo, anemia or significant lab/ecg abnormalities, investigational drugs or partiipation in a clinical trial in last mo, treatment with any other diabetes med (besides met) in past 8 wk, tx with potent CYP 450 3A drug or contradindicated to or history of treatment with saxagliptin
Forst, 2010[57] Europe NCT00881530	Neither year reported 12 Wks	Yes	Not Extracted	Yes	NR/ 333 NR	Age <21 or >75 yrs, HbA1c >9.0% for patients previously treated with met and one other oral anti-diabetic drug; 10.0% for patients perviously treated with met alone; 10% for all patients after run-in phase or <7.0% for patients previously treated with met and one other oral anti-diabetic drug; 7.5% for patients previously treated with met alone; 7.5% for all patients after run-in phase, BMI <25 or >40 kg/m2, <3 months, Prior or current use of insulin, previously treated with therapy other than 1. met alone; 2. met and one other oral hypoglycaemic agent other than rosi or pio., anti-diabetic therapy changed within 10 wks prior to screening, FPG concentrations > 13.3mmol/l (measured on 2 separate days), treated with rosi or pio within 6 months prior to screening, one or more of a list of specified clinical lab abnormalities (not specified in article), clinically relevant stroke, MI, TIA within 6 months
Forst, 2012[58] NR NCT01593371	Neither year reported 12 Wks	No	Not Extracted	Yes	NR/ 44 NR	Age <30- > 65 yrs, HbA1c < =7%, Retinopathy, not on metformin, receiving any other anti-diabetic drugs, SBP >160 mmHg, DBP >90 mmHg, GFR <60, Smoking in last 6 months

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Forst, 2014[59] Germany No	Neither year reported 12 Wks	No	Not Extracted	Yes	NR/ 40 outpatient but unclear if primary or specialty care	Age <45 or >75yrs, HbA1c >8.5% or <6.5%, Any liver disease, Any kidney disease, more than one unexplained episode of severe hypoglycaemia within 6 months, pre-treatment with anti-diabetic drugs other than metformin within the last 3 months, uncontrolled hypertension (SBP>160mmHg, and/or DBP>90mmHg), MI or stroke in last 6 month
Gallwitz, 2011[60] Germany NCT00885378	Neither year reported 26 Wks	No	Not Extracted	Yes	NR/ 363 NR	Adults, HbA1c >10% or <6.5%, not on metformin
Gallwitz, 2012[61] Multi-continent NCT00562172	2008 2010 104 Wks	Yes	Not Extracted	Yes	NR/ 1552 Outpatient: primary care Outpatient: subspecialty care setting	Age <18, >80 yrs, BMI >40 kg/m^2, Prior or current use of insulin, Any liver disease, History of CVD, Not on stable metformin dose >= 1500mg/day (alone or with another antidiabetic drug), HbA1c <6.5% or >10% if participant on metformin alone prior to enrollment, HbA1c <6% or >9% if participant on metformin and another anti-diabetic medication prior to enrollment, myocardial infarction, stroke, transient ischemic attack 6 months prior to screening, treatment with rosiglitazone, pioglitazone, GLP-1 analogue or agonist 3 months prior to screening, On anti-obesity drug in 3 months prior to screening
Gallwitz, 2012[62] Multi-continent No	2006 2011 48 Months	No	Not Extracted	Yes	NR/ 1029 NR	Age <18 or >85 yrs, HbA1c >9% or <6.5%, BMI <25 or >=40 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, adequate response to metformin based on HbA1c criteria, contraindication to glimepiride, active/untreated cancer or cancer in remission <5 yrs, hemoglobinopathy or significant anemia, severe GI disease, on drugs affecting motility, glucocorticoids, weight loss drugs in last 3 mo, treatment for more than 2 wks in past 3 mo with insulin, TZDs, alpha glucosidase inhib, SUs, meglitinides

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Garber, 2002[63] US Not extracted	Not extracted 20 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, treatment experienced, HbA1c <7% or >11%, no Type 2 DM, other
Garber, 2003[64] US Not extracted	Not extracted 16 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <20 or >79 yrs, any liver disease, any kidney disease, treatment experienced, HbA1c >7% or <12%, no Type 2 DM, other
Garber, 2006[65] US Not extracted	Not extracted 24 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <20 or >78 yrs, any liver disease, any kidney disease, history of CVD, HbA1c ≤7% or ≥12% no Type 2 DM, other
Garber, 2009[66] US, Mexico Not extracted	Start year 2006 End year 2007 52 wks	Fewer than 10 % participants excluded during run-in period	< 6 months	Yes	NR/746 NR	Age <18 or >80 yrs, HbA1c <7% or >11% if prior treatment was diet; >10% if prior treatment was drug, BMI >45 kg/m^2, either not treated with diet and exercise or up to half the highest dose of oral antidiabetic drug monotherapy for at least 2 months prior to trial, insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia, impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations 5 times upper normal range)
Garber, 2011[67] US Mexico No	2006 2008 104 Wks	No	Not Extracted	Yes	NR/ 746 NR	Age <18 or >80 yrs, HbA1c >11% if on diet/exercise or >10% if on monotherapy or <7%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Genovese, 2013[68] Italy NCT00511108	Neither year reported 24 Wks	Yes	Not Extracted	Yes	NR/ 213 NR	Age <35 or >75 yrs, Any liver disease, Any kidney disease, Pregnant, Nursing, Not using adequate contraception, not taking metformin (2000-30000mg/day) for at least 3 months, HDL-C levels >=40mg/dl in males and >=50mg/dl in females irrespective of statin tx, anemia of any etiology (Hb<10.5g/dl) or any other hematological disease; diagnosis or suspicion of neoplastic disease, no central obesity (excluded if waist circumference <94 cm for men and <80 cm for women), using oral anti-diabetic drugs other than met or insulin in the 3 months preceding study entry, treatment with fibrates or rifampicin, acute or chronic pancreatitis or familial polyposis, history of chronic alcohol or drug/substance abuse, satisfactory drug compliance (compliance ranging between 80-120%) during run-in, medical history of MI, transient ischemic attacks or stroke in the past 6 months, designation of class 1-4 heart failure according to NYHA criteria
Genovese, 2013[69] Country NR No	Neither year reported 16 Wks	Yes	Not Extracted	Yes	NR/ 58 Outpatient: subspecialty care setting	Age <35 or >75 yrs, HbA1c >9.00%, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, lack of cooperative attitude and ability to be treained to use the investigational drugs correctly or to attain the study procedures, participation in another trial in the 3 months preceding study entry, any disease with malabsorption, or familial polyposis or pancreatitis, CHF (NYHA class 1-4), anemia of any etiology (hemoglobin level < 10.5g/dl) or any other clinically relevant hematologic disease, diagnosis or suspicion of any neoplastic disease, history of chronic alcohol or drug/substance abuse, or presence of other conditions potentially able to affect study stubjects compliance, concomitant therapy with statins, antioxidant drugs (e.g. vitamins, Q10 coenzyme), beta-blockers, nonsteroidal anti-inflammatory drugs, aspirin, corticosteroids,, known allergy, sensitivity, ,or intolerance to study drugs and/or study drugs' formulation ingredients (pioglitazone, met marked above)

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Goke, 2010[70] Multi-continent No	2007 2010 104 Wks	Yes	Not Extracted	Yes	NR/ 858 NR	Age <18 yrs, HbA1c >10% or <6.50%, Prior or current use of insulin, Prior or current use of study drug, Any liver disease, Any kidney disease, no type 2 diabetes, not on stable metformin monotherapy >=1500mg/day for at least 8 wks prior to enrollment, type 1 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, donation of blood, plasma or platelets within the 3 months prior to enrolment, history of haemoglobinopathies; significant alcohol or drug abuse within the year prior to enrolment, treatment with human immunodeficiency virus Γüä antiviral drugs or cytochrome P450 3A4 (CYP450 3A4) inducers, treatment with a thiazolidinedione within 12 wks prior to enrollment, congestive heart failure, significant cardiovascular history within the past 6 months
Goldstein, 2003[71] US Not extracted	Not extracted 18 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% and >12.0%, other
Goldstein, 2007[72] Multi-continent Not extracted	Neither year reported 24 Wks	Run-in period but number excluded was NR	NR	Yes	3544/1091 NR	Age <18 or >78 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), patient with less than 75% compliance during placebo run in period, patient with HbA1c <7.5% or >11 % after diet/exercise run in/wash-out period, patients with fasting glucose >280 mg/dl after run-in period, no Type 2 DM, Type 1 DM
Gomez-Perez, 2002[73] Mexico Not extracted	Not extracted 26 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Gupta, 2009[74] NR Not extracted	Neither year reported 16 Wks	No run-in period	< 6 months	Yes	247/51 NR	Age <35 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), pregnant, not using adequate contraception, FPG >200 mg/dL, individuals using orlistat, sibutramine, ephedrine, steroids, significant lung diseases, significant neurologic diseases, baseline BP>140/90 mmHg, prior use of TZD, beta blockers, smokers, alcohol abuse and using drugs, patients using metal objects precluding required scans
Gupta, 2010[75] India NCT00772174	Neither year reported 12 Wks	No	Not Extracted	NR	NR/ 94 Outpatient: subspecialty care setting	Age <30 yrs , Any kidney disease, History of CVD, Pregnant, Nursing, history of serious or hypersensitivity reactions to any of study drugs, uncontrolled hyper tension, HF NYHA class IV, recent unstable angina, MI, coronary artery bypass surgery, angioplasty within previous 2 months, TIA, cerebrovascular accident, oral contraceptive use, chronic alcohilism
Gupta, 2013[76] India NCT00363948	2012 2013 24 Wks	No	Not Extracted	NR	NR/ 167 Outpatient: primary care	Any liver disease, Any kidney disease, Pregnant, Nursing, history of hypersensitivity to sulphonylurea and DPP-IV inhibitors, psychiatric, GI, hematological, metabolic, neurological, hepatic, or renal disorders, clinically significant heart disease (NYHA III or IV), acute infection

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Haak, 2012[77] Multi-continent ACTRN12608000534381	2008 2010 24 Wks	Yes	Not Extracted	Yes	NR/ 791 NR	Age <18 or >80 yrs, HbA1c >10.5% if on OAD or >=11% if treatment naïve or <7.0% if on OAD or <7.5% if treatment naïve, BMI > 40 kg/m2, Prior or current use of insulin, Any kidney disease, History of CVD, Pregnant, Nursing, neither treatment naive nor had been treated with OAD monotherapy, prior treatment with rosiglitazone, pioglitazone, GLP-1 analogs, or anti-obesity drugs in the previous 3 months, receiving treatment with systemic steroids or had a change in dosage of thyroid hormones in the previous 6 wks, had undergone gastric bypass, Had known hypersensitivity or allergy to linagliptin or its excipients, metformin or placebo, had a history of alcohol or drug abuse in the previous 3 months, had acute or chronic metabolic acidosis, had hereditary galactose intolerance, had experienced a myocardial infarction, stroke, or transient ischemic attack in the previous 6 months
Haak, 2013[78] Multi-continent IRCT201102275917N1	2009 2011 52 Wks	Yes	Not Extracted	Yes	NR/ 567 NR	Pregnant, Nursing, Not using adequate contraception, completed the previous 6-month trial, were not on rescue medication, alcohol abuse within the past 3 months or drug abuse that would have interfered with trial participation
Hallsten, 2002[79] Finland Not extracted	Not extracted 26 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hamann, 2008[80] Multinational Europe, Mexico Not extracted	Neither year reported 52 Wks	Yes	< 6 months	NR	818/596 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >10%, BMI <25 kg/m^2, used any oral antidiabetic drug other than metformin in the prior 12 wks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin <11.0 g/dl for men and <10.0 g/dl for women), C-peptide <0.5nmol/L, SBP >170mmHg, DBP >100mmHg
Hanefeld, 2004[81] Canada, UK, Hungary, Finland, Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and the Netherlands Not extracted	Not extracted NR	Not extracted	Not extracted	Yes	Not extracted	Age <35 or >75 yrs, history of CVD, HbA1c <7.5% or >11%, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hanefeld, 2007[82] Multinational Europe Not extracted	Neither year reported 52 Wks	Run-in period but number excluded was NR	< 6 months	Yes	NR/598 NR	Age <40 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI <22 kg/m^2 or >38 kg/m^2, pregnant, patient on insulin therapy, patient with diabetic complications requiring treatment, hematologic impairment, FPG < 7mmol/l or >15 mmol/l, C peptide <0.27 nmol/l
Haring, 2014[83] Multi-continent NCT00509262	2010 2012 24 Wks	Yes	Not Extracted	Yes	NR/ 638 NR	Age <18 yrs, HbA1c >10% or <7%, BMI >45 kg/m2, Any liver disease, Contraindication or history of intolerance to metformin, not on stable MFM IR unchanged >=12 wks prior to randomization, uncontrolled hyperglycemia (glu> 13.3mmol/L) after overnight fast confirmed by 2nd measurement, ACS, stroke, TIA within 3 mo, bariatric surgery or other GI surgeries that induce chronic malabsorption, cancer (except basal cell ca) or tx for CA within last 5 yrs, blood dyscrasias, hemolysis, unstable erythrocytes, tx with antiobesity drugs 3m prior, use of tx leading to unstable body weight, tx with systemic steroids, change in dose of thyroid hormones within 6w, alcohol or drug abuse within 3m, investigational drug in another trial with 30d, eGFR<30
Henry, 2012[84] Multi-continent NCT00754988	2008 2009 24 Wks	Yes	Not Extracted	Yes	NR/ 603 Inpatient/hospital Outpatient: primary care Outpatient: subspecialty care setting	Age <18 or >77 yrs, HbA1c >12% or <7.5%, BMI >45 kg/m2, Any liver disease, Any kidney disease, creatine kinase > 3 times ULN, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), NYHA Class III or IV congestive heart failure, SBP ΓÇí 180 or DBP ΓÇí 110 mmHg., a cardiovascular event within 6 months, other significant renal, hepatic, hematologic, oncologic, endocrine, psychiatric, or rheumatic disease

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Henry, 2012[84] Multi-continent No	2009 2010 24 Wks	Yes	Not Extracted	Yes	NR/ 641 Inpatient/hospital Outpatient: primary care Outpatient: subspecialty care setting	Age <18 or >77 yrs, HbA1c >12% or <7.5%, BMI >45 kg/m2, Any liver disease, Any kidney disease, History of CVD, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), NYHA Class III or IV congestive heart failure, SBP ΓÇí 180 or DBP ΓÇí 110 mmHg., a cardiovascular event within 6 months
Hermann, 1991[85] Sweden Not extracted	Not extracted 6 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	No Type 2 DM, other
Hermann, 1991[85] Sweden Not extracted	Not extracted 6 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other
Hermann, 1994[86] Sweden Not extracted	Not extracted 6 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	No Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Hermans, 2012[87] Europe NCT01006590)	Neither year reported 24 Wks	Yes	Not Extracted	Yes	NR/ 286 NR	Age <18 yrs, HbA1c >10% or <7%, Prior or current use of insulin, Contraindication or history of intolerance to metformin, Pregnant, Nursing, type 1 DM, history of DKA or HONC, prior use of injectable GLP-1 analogues within 3mo of study, treatment with systemic glu- cocorticoids other than replacement therapy (inhaled, local injected and topical use of glucocorticoids were allowed), treatment with cytochrome P450 3A4 inducers, not on stable tx with metfomrin 1500-1700 mg/d
Home, 2007[88] Multinational Europe, Australia and New Zealand Not extracted	Start year 2000 End year 2002 18 Months	Run-in period but number excluded was NR	>= 6 months	NR	7428/4458 NR	Age <40 or >75 yrs, HbA1c <7% or >9%, BMI <25 kg/m^2
Home, 2009[89] Multinational Europe Not extracted	Start year 2001 End year 2003 7.5 Years	Run-in period but number excluded was NR	>= 6 months	Yes	7428/4458 Outpatient primary care	Age <40 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), contraindication or history of intolerance to metformin, history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or >9%, BMI <25 kg/m^2, pregnant, nursing, not using adequate contraception
Iliadis, 2007[90] Greece Not extracted	Neither year reported 18 Wks	Run-in period but number excluded was NR	NR	NR	NR/48 Outpatient subspecialt y care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), diagnosis of Type 2 DM >3 yrs, use of any diabetes medication, no Type 2 DM, any heart failure

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jadzinsky, 2009[91] Multi-continent Not extracted	Start year 2006 End year 2008 24 wks	Fewer than 10% participants excluded during run-in period	< 6 months	Yes	2936/1394 Outpatient Primary care setting	Age <18 or >77 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), HbA1c <8% or >12%, BMI >40 kg/m^2, prior treatment, diabetic ketoacidosis or nonketotic hyperosmolar coma, CV events 6 months prior, LVEF <40%, psychiatric history, alcohol or drug abuse, abnormal metabolic or hematologic test
Jain, 2006[92] US, Puerto Rico Not extracted	Neither year reported 56 Wks	Run-in period but number excluded was NR	< 6 months	NR	NR/502 NR	Age <18 or >80 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), HbA1c <7.5% or >11.5%, pregnant, nursing, duration of diabetes > than 2 yrs, intolerance to rosiglitazone, pioglitazone, or troglitazone, drug or alcohol abuse, previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin, SU for 3 months or more, use of hydrochlorothiazide, joint injections, niacin greater than 250 mg /day, oral anti-diabetic drugs, concurrent participation in another investigational study, serum creatinine level >1.5 mg/dl for men, 1.4 mg/dl for women, 1+ proteinuria, anemia (<10 g/dl women, <12 g/dl men), BMI ≤20 kg/m^2 or >45 kg/m^2; hypertension, chronic pulmonary disease, history of cancer not in remission for at least 5 yrs
Ji, 2015[93] Multi-continent NCT01438814	Start year 2011 End year 2013 14 wks	Run-in period but number excluded was NR	NR	Yes	NR/689 NR	Age <18 or >80, HbA1c>10, HbA1c 7, BMI or weight >45, prior use of any diabetes treatment, prior or current use of insulin, prior or current use of study drug, any liver disease, any kidney disease, contraindication or history of intolerance to metformin, pregnant, nursing, bariatric surgery, cancer, blood dyscrasias, pancreatitis, treatment with anti-obesity drugs within 3 months before consent or any other treatment at the time of screening leading to unstable body weight, glucose >240 mg/dl, acute coronary syndrome, stroke, or transient ischemic attack within 3 months before consent, treatment with systemic steroids, change in dosage of thyroid hormones within 6 weeks

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Jonker, 2009[94] Netherlands Not extracted	Neither year reported 24 wks	Run-in period but number excluded was NR	< 6 months	Yes	173/78 Outpatient Primary care setting	Age <45 or >65 yrs, female, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c <6.5% or >8.5%, BMI <25 kg/m^2 or >32 kg/m^2, no Type 2 DM, prior use of TZD/insulin, BP >150/85 mm Hg
Kadoglou, 2011[95] Greece No	2006 2008 6 Months	No	Not Extracted	No	NR/ 140 NR	Age <50 and >75 yrs, HbA1c <=7%, BMI <=25kg/m2, Any liver disease, Any kidney disease, usage of antidiabetic medications, autoimmune or life threatening illnesses, on diet therapy for diabets for at least 3 mo, CHF (NYHA class IIIV), clinical evidence of cardiovascular (coronary, peripheral arteries), autoimmune or life-threatening diseases, alcohol / drug abuse, uncontrolled hypertension (blood pressure > 170 / 100 mmHg), recently diagnosed / or untreated hormonic disorders, free from microvascular compl, maintained body weight for 3 mo before study
Kadowaki, 2013[96] Japan No	2006 2008 12 Wks	Yes	Not Extracted	Yes	NR/ 149 NR	Age <20 or >=75yrs, HbA1c >9.4% for patients receiving an OHA other than metformin at screening, >10.5% for patients with metformin only at screening, >10.5% for all patients completing the run-in period, or <6.4% for patients receiving an OHA other than metformin at screening, 6.9% for patients with metformin only at screening, 6.9% for all patients completing the run-in period, Any kidney disease, high serum creatinine levels (male > 100.8umol/l, female>78.7umol/l), FPG>15.0mmol/l at the beginning of the placebo run-in period, not on stable diet and exercise therapy for at least 8 wks, not on met monotherapy for at least 12 wks
Kahn, 2006[97] Multi-continent Not extracted	Start year 2000 End year 2006 6 Years	No run-in period	NR	Yes	6676/4360 NR	Age <30 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), uncontrolled hypertension, FPG <126 or >180 mg/dL, history of lactic acidosis

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kaku, 2009[98] Japan Not extracted	Start year 2005 40 Wks	Yes	< 6 months	Yes	NR/236 NR	Age ≤ 20 and ≥65 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), HbA1c <6.5% or >10%, other pre-existing conditions that potentially require hospitalization such as cancer, severe lung, GI, pancreatic and hematological disorders, history of lactic acidosis, ketoacidosis, diabetic coma, or pre-coma within the preceding 26 wks, if on any medications that might affect glycemic control, drug or alcohol dependency
Kaku, 2011[99] Japan No	2006 52 Wks	Yes	Not Extracted	Yes	NR/ 411 NR	Age <20 yrs, HbA1c >10.4% or <7.4%, not able to self monitor blood glucoses
Kato, 2009[100] Multinational Europe Not extracted	Neither year reported 12 wks	No run-in period	NR	NR	NR/50 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, no Type 2 DM, no metabolic syndrome, not on continuous diet/exercise therapy, no anemia, no history of heart failure
Kikuchi, 2012[101] Japan NCT00359762, EudraCT 2005-005448-21	2005 2007 28 Wks	No	Not Extracted	Yes	NR/ 373 NR	Age <20 - >75 yrs, HbA1c <7.4%, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Retinopathy, hyperlipidemia w/o statin tx, SBP >=160 or DBP >=100, FPG >=270, BNP >= 60, hemoglobinopathy, edema, unstable or serious angina, MI in past year, h/o or current heart failure, serious arrhythmia, valvular dis, cardiomyopathy, serious neuropathy requiring tx

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Kim, 2007[102] South Korea Not extracted	Neither year reported 12 Wks	Fewer than 10% of participants were excluded during run-in	< 6 months	No	NR/120 Outpatient primary care, Outpatient subspecialty care setting	Age <30 or >70 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), duration of diabetes >5 yrs, not on a stable medication with a SU and/or alpha glucosidase inhibitor for at least 3 months, episodes of ketonuria or ketoacidosis, current malignancy, tuberculosis, rheumatic disease, thyroid disease, corticosteroid treatment, previous TZD or metformin treatment
Kim, 2014[103] South Korea NCT00751114	2007 2009 26 Wks	Yes	Not Extracted	Yes	NR/ 209 NR	HbA1c >10% or <7%, , Pregnant, treated with metformin 500-1000mg alone for at least 4 wks prior to study, unable to complete diary to monitor SMBG, acute complications such as diabetic ketoacidosis, hyperglycemic hypoerosmolar state within 3 months, clinically significatn renal or hepatic disorders
Kiyici, 2009[104] Turkey Not extracted	Neither year reported 52 wks	No run-in period	< 6 months	No	NR/50 Outpatient subspecialty care setting	Age <30 or >65 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >8%, BMI >40 kg/m^2, GI disease, rheumatological, or neoplastic, infectious diseases, history of using anti-diabetic medications, any endocrine disease except diabetes or hyperlipidemia, smoking, microvascular complications of diabetes, history of substance abuse
Kvapil, 2006[105] Multinational Europe Not extracted	Neither year reported 16 Wks	No run-in period	< 6 months	NR	NR/341 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, recurrent severe hypoglycemia, anemia, change in dose of meds known to interfere with glucose metabolism, inclusion criteria is not adequately controlled on metformin

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Lavalle-Gonzalez, 2013[106] Multi-continent NCT00813995	Neither year reported 56 Wks	Yes	Not Extracted	Yes	NR/ 1284 NR	Age <18 or >80 yrs, HbA1c >10.5% or <7%, Prior or current use of insulin, Any kidney disease, not on MFM (ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose], repeated FPG and/or fasting self-monitored blood glucose (SMBG) ГëÑ15.0 mmol/l during the pretreatment phase, Type 1 diabetes, treatment with a peroxisome proliferator-activated receptor ╬│ agonist, insulin, another SGLT2 inhibitor or any other AHA (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 wks before screening;, CVD(including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening, uncontrolled HTN
Lawrence, 2004[107] UK Not extracted	Not extracted 12 titration and 12 maintenance wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <45 or >80 yrs, any liver disease, any kidney disease, history of CVD, HbA1c for diet treated diabetes <7% or >10% and for low-dose ODM >7.5%, no Type 2 DM, other
Leiter, 2005[108] Canada Not extracted	Neither year reported 32 Wks	No run-in period	< 6 months	Yes	720/613 Outpatient primary care	Age <20 or >80 yrs, HbA1c <9.5%, no Type 2 DM, FBG <7 and >14 mmol/l
List, 2009[109] US Canada, Mexico, Puerto Rico NCT00297063	2005 2006 12 Wks	Yes	Not Extracted	Yes	NR/ 389 "98 clinical centers"	Age <18 or >79 yrs, HbA1c >10% or <7%, BMI >40 kg/m2, Prior use of any diabetes treatment, Any kidney disease, C peptide>1.0 ng/ml

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Madsbad, 2004[110] Multinational Europe Not extracted	Start year 2000 End year 2001 12 wks	No run-in period	< 6 months	Yes	311/193 Outpatient Primary Care setting	Age <30 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), HbA1c < 7.5% or >10% on diet treatment, BMI >40 kg/m^2, pregnant, nursing, not using adequate contraception, no Type 2 DM, no treatment for DM with ODM or diet, HbA1c >9.5% on ODM, history of CHF, NYHA class III, IV, use of TZDs or other investigational drugs
Maffioli, 2013[111] Italy NCT 01208012	Neither year reported 6 Months	Yes	Not Extracted	No	NR/ 170 outpatient care - unclear if specialty or primary care	Age <18 yrs, HbA1c <8.0%, BMI < 25.0 or >34.9 kg/m2, Prior use of any diabetes treatment, Any kidney disease, History of CVD, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, does not have hepatic steatosis by ultrasound diagnosis, history of ketoacidosis, muscle toxicity, serum creatine phosphokinase values higher than 2 times the ULN, severe anemia, known contraindications to pioglitazone, glibenclamide, or HMG-CoA inhibitors
Malone, 2003[112] 14 countries not specified Not extracted	Neither year reported 16 Wks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/597 subgroup completing test	Age <30 or >75 yrs, HbA1c <125% of upper limit of normal by local lab within 4 wks prior to entry, BMI >40 kg/m^2, not Type 2 DM, not use of single oral agent (metformin or SU) for 3 months prior to study at maximum clinically effective dose for previous 30 days

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Marre, 2002[113] Netherlands, Denmark, Portugal, France, Belgium Not extracted	Not extracted 4 months (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 yrs, any liver disease, any kidney disease, history of CVD, other
Moon, 2014[114] Korea NCT00676338	2007 2009 48 Wks	Yes	Not Extracted	Yes	NR/ 75 NR	Age <18 or >75 yrs, HbA1c >12.00% or <7.50%, BMI>=35kg/m2, Any liver disease, Any kidney disease, not on metformin monotherapy (at a dose of >1000mg/day for 3 months prior to enrollment), Taking medications (other than antidiabetic medications) known to affect glycemic control such as glucocorticoids
Nakamura, 2000[115] Japan Not extracted	Not extracted 3 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Any liver disease, history of CVD, treatment experienced, HbA1c <6.5%, no Type 2 DM, other
Nakamura, 2004[116] Japan Not extracted	Neither year reported 12 Months	No run-in period	>= 6 months	NR	NR/45 Inpatient/hospital	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >6.5%, BP <140/90 mm Hg, controlled on diet alone, C-peptide <0.33 mmol/l, creatinine <1.5 mg/dL, no antihypertensive medications, malignancy, no microalbuminuria, collagen vascular disease, non-diabetic renal disease
Natali, 2004[117] London and Italy Not extracted	Not extracted 16 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c >10% after washout, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Nauck, 2007[118] US, Multinational Europe, Multi-continent Not extracted	Neither year reported 52 Wks	Yes	< 6 months	Yes	2141/1172 NR	Age <18 or >78 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15 mmol/L, insulin use within 8 wks of screening, history of Type 1 DM, other treatments for hypoglycemia
Nauck, 2009[119] Multi-continent NCT00960076	Neither year reported 26 Wks	Yes	Not Extracted	Yes	NR/ 527 NR	Age <18 or >80 yrs, HbA1c >10.00% or <7.00%, BMI <23 or >45 kg/m2, Any kidney disease, used antidiabetic agents other than met within the 3 months prior to screening, or not on ongoing (>=3 months) stable metformin monotherapy regimen (>=1500mg per day for at least 8 wks), C-PEPTIDE CONCENTRATION <0.26 nmol/l, use of steroids or weight loss meds in last 3 months, after run-in/stabilisation period FPG>=275mg/dl, during run-in/stabilisation peiod <75% compliance with the single-blind placebo regimen, h/o cardiac surgery or CVDin last 6 months, history of cancer (other than squamous cell or basal cell carcinoma of the skin that had not been in full remission for at least 5 yrs), laser treatment for proliferative diabetic retinopathy within 6 months, history of treated diabetic gastroparesis, NYHA Class 3 or 4 heart failure
Nauck, 2011[120] Multi-continent NCT00393718	2008 52 Wks	Yes	Not Extracted	Yes	NR/ 814 NR	Age < 18 yrs, HbA1c >10% or <6.50%, BMI > 45.0 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, not taking metformin +/- another oral antidiabetes drug, FPG > 15 mmol/L; C-peptide < 0.33 nmol/L, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; polyuria/polydipsia with > 10% weight loss, calculated creatinine clearance < 60 mL/min; urine albumin:creatinine ratio > 203.4 mg/mmol, AST and/or ALT and/or creatine kinase >= 3x ULN; serum total bilirubin > 34 micromol/L, Hb <= 11 g/dL for men and <= 10 g/dL for women; abnormal thyroid stimulating hormone level, SBP >= 180 mmHg and/or DBP >= 110 mmHg, cardiovascular event in last 6 months, CHF, significant respiratory, hematological, oncological, endocrine, immunological, and alcohol and/or substance misuse disorders, use of systemic corticosteroids equivalent to >10 mg of oral prednisolone within 30 days of enrolment, history of bariatric surgery; use of weight loss medication within 30 days or enrolment

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Nauck, 2014[121] Country NR No	 Neither year reported 52 Wks	Yes	Not Extracted	Yes	NR/ 1098 NR	Age <18 or >75 yrs, HbA1c >= 9.5% or <8% if on diet and exercise alone or <7% if on OAD monotherapy or combination therapy, BMI <25 or >40 kg/m2, Prior or current use of insulin, Prior or current use of study drug, unstable weight during the 3-months prior to study entry
Oz Gul, 2010[122] Turkey UMIN000004582	 Neither year reported 12 Wks	No	Not Extracted	NR	NR/ 60 NR	Prior use of any diabetes treatment, Prior or current use of study drug, Any liver disease, Any kidney disease, History of CVD, Pregnant, Nursing, cerebrovascular conditions, impaired kidney function, statins, ACE inhibitor use, need of insulin for acute complications, any medications known to affect sRAGE metabolism
Pavo, 2003[123] Russia and Hungary Not extracted	Not extracted 32 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <7.5% or >11.0%, no Type 2 DM, other
Perez-Monteverde, 2011[124] Country NR NCT00661362	 Neither year reported 12 Wks	Yes	Not Extracted	Yes	NR/ 492 NR	Age <18 - >78 yrs, HbA1c >12% or <7.5%, Contraindication or history of intolerance to metformin, type 1 Diabetes, history of ketoacidosis, symptomatic hyperglycemia, hypersens or contraind to study drug, not taking an antihyperglycaemic agent (AHA) within the previous 3 months and not more than 4 wks cumulatively in the previous 3 year, likely to need a drug that is a CYP2C8 inhib or inducer, symptomatic hyperglycaemia or a site fingerstick glucose < 130 mgГüä dl or > 320 mgГüä dl at the randomisation visi

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Perez, 2009[125] US, multinational Europe Not extracted	Neither year reported 24 wks	Run-in period but number excluded was NR	< 6 months	Yes	1436/600 NR	Age <18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), contraindication or history of intolerance to metformin, HbA1c <7.5% or >10%, BMI >45 kg/m^2, pregnant, nursing, triglycerides >500 mg/dL, discontinued metformin and TZD therapy due to lack of efficacy
Petrica, 2009[126] Romania NCT00097500	Neither year reported 12 Months	No	Not Extracted	No	NR/ 44 Outpatient: subspecialty care setting	HbA1c <7%, no poor glycemic control with previous medication, no stable therapy with metformin for at least 6 months, CKD of non-diabetic origin, symptoms or history of cerebrovascular disease (TIA, stroke), micro/macroalbuminuria, thyroid dysfunction, abnormal albuminuria, microangiogrpahic complications
Pfutzner, 2005[127] Germany Not extracted	Not extracted 26 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >75 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <6.6% or >9.9%, other
Pfutzner, 2011[128] Germany (assumed based on author affiliations) NCT00541450	Neither year reported 24 Wks	No	Not Extracted	Yes	NR/ 305 NR	Age <18 - >75, HbA1c <6.5%, Any liver disease, Any kidney disease, History of CVD, Pregnant, patients without dyslipidemia, Prior use of any diabetes treatment except for metformin, no current treatment MET, respiratory, neurological or hematlogical disease, not on individually-determined maximal metformin, hypersensitivity to study drugs, history of severe or multiple allergies, h/o significant CVD (greater than NYHA stages II-IV)

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Pfutzner, 2011[129] Multi-continent NCT00386100	Neither year reported 76 Wks	Yes	Not Extracted	Yes	NR/ 1306 Community outpatient settings (unspecified)	Age <18 or >77 yrs, HbA1c >12.00% or <8.00%, BMI >40 kg/m2, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, fasting C-peptide < 1.0 ng/ml, symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, CVD event within the prior 6 months or NYHA stage III/IV CHF and/or LVEF </= 40%, psychiatric disorder, alcohol or drug abuse within previous year, treatment with potential CYP3A4 inhibitors or inducers, immunocompromised individuals, clinically signficant abnormal hepatic, renal, endocrine, metabolic or hematological screening tests
Pratley, 2010[130] Multi-continent Europe, US, and Canada Not extracted	Start year 2008 End year 2009 26 months	No run-in period	>= 6months	Yes	1302/665 "Office-based"- possibly out patient	Age <18 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >7.5% or <10%, BMI >45 kg/m^2, no Type 2 DM, cancer, contraindication to trial drugs, recurrent hypoglycemic or hypoglycemia unawareness, not on metformin for at least 3 months, on any non-metformin anti-hypoglycemic in past 3 months
Pratley, 2014[131] Multi-continent No	Neither year reported 26 Wks	Yes	Not Extracted	Yes	784 NR	Age <18 yrs or >80 yrs, HbA1c >10% or <7.50%, BMI <23 or >45 kg/m2, <20 or >35 kg/m2 for Asian participants, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, Not using adequate contraception, class 3 or 4 CHF OR recent CVD event in last 3 months such as MI, stent, bypass, adequate controlled glycemia following treatment with diet and exercise alone for at least 2 months prior to screening, fasting C-peptide concentration < 0.8ng/ml (0.26nmol/l), lack of ability or willingness to monitor blood glucose using a home glucos monitor and keep a glucose diary, at week-1 of the placebo run-in/stabilization period prior to randomization: HbA1c<7.5% or >10%, at week-1 of the placebo run-in/stabilization period prior to randomization: study drug compliance < 75% or >125%, at week-1 of the placebo run-in/stabilization period prior to randomization: use of oral or systemically injected glucocorticoids or weight-loss drugs, low hemoglobin levels (Гёñ 12 and Гёñ 10 g/dL for men and women, respectively), elevated blood pressure (ГёÑ 150 and ГёÑ 90 mm Hg for systolic and diastolic, respectively), hemoglobinopathy

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Qiu, 2014[132] Multi-continent No	Neither year reported 22 Wks	Yes	Not Extracted	Yes	NR/ 279 NR	Age <18 or >80 yrs, HbA1c >10.5% or <7%, Any kidney disease, FPG and/or fasting self-monitored blood glucose 15.0 mmol/L during the pretreatment phase, diabetic ketoacidosis, history of CVD(including myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident) within 3 months before screening, un- controlled hypertension, not on metformin monotherapy at protocol-specified doses (at least 1500 mg/d (>2000 mg/d preferred), on any other diabetes medication within last 12 wks, not completing the placebo run-in period
Ramachandran, 2004[133] India Not extracted	Not extracted 14 wks (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <30 or >60 yrs, treatment experienced, HbA1c >11%, no Type 2 DM, other
Raskin, 2007[134] US Not extracted	Neither year reported 28 Wks	Run-in period but number excluded was NR	< 6 months	NR	N/NR NR	Age <18 or >75 yrs, HbA1c ≤8.0%, BMI >40 kg/m^2 or weight >125 kg (275lbs), pregnant, nursing, not using adequate contraception, if not on metformin ≥1,000mg /day as a single agent or in ODM combination therapy for at least 3 months before the trial, history of insulin use
Reasner, 2011[135] US NCT00770653	2007 2009 44 Wks	Yes	Not Extracted	Yes	NR/ 1250 NR	Age <18 or >78 yrs, HbA1c <7.5%, Prior use of any diabetes treatment, Any liver disease, History of CVD, Contraindication or history of intolerance to metformin, No type 2 diabetes, Not on diet/exercise regimen, Finger stick glucose test <7.2 or >17.8 mmol/l, Type 1 diabetes
Ridderstrale, 2014[136] Multi-continent NCT00770653	2010 2011 104 Wks	Yes	Not Extracted	Yes	NR/ 1549 NR	Age <18 yrs, HbA1c >10% or <7%, BMI >45 kg/m2, Any kidney disease, not on stable dose of MFM IR (>=1500mg/day or max tolerated dose, or max dose according to local label) for at least 12 wks prior to randomization, blood glucose concentration greater than 13 ┬┴ 3 mmol/L after an overnight fast during the placebo run-in, confi rmed by a second measurement, use of antidiabetes drugs other than metformin immediate release any time during the 12 wks before randomisation

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rigby, 2009[137] US, Multicontinent Not extracted	Start year 2007 End year 2008 16 months	No run-in period	< 6 months	Yes	356/169 NR	Age <18 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% (6.5% if on metformin combination therapy) or >10% (9.5% if on metformin combination therapy), BMI > 40 kg/m^2, LDL <50 mg/dL or triglycerides ≥500 mg/dL, weight loss program with ongoing weight loss or starting an intensive exercise program within 4 wks of screening, need for oral corticosteroids, bile acid sequestrants, or any antidiabetes medications other than metformin, >2months insulin, not on metformin for ≥3 months (1500-2550 mg/day), Type 1 DM and/or ketoacidosis, dysphagia/swallowing disorders, intestinal motility disorders, pancreatitis, HIV/AIDS, drug/alcohol abuse within 2 yrs, any serious disorder including pulmonary, hepatic, GI, uncontrolled endocrine/metabolic, hematologic/oncologic (within 5 yrs), neurologic, or psychiatric diseases, current treatment with TZD/combo with metformin/colesevelam/fixed-dose combination product including metformin, hospitalization within 14 days of screening
Robbins, 2007[138] US, Multinational Europe, Multi-continent, India, Australia Not extracted	Neither year reported 24 Wks	Run-in period but number excluded was NR	< 6 months	NR	433/317 NR	Age <35 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <6.5% or >11%, pregnant, nursing, not using adequate contraception, patients who were receiving continuous SC insulin injections or a total daily insulin of >2.0 U/kg or who had a change in type or dose of lipid-altering medications or TZD use up to 3 months before the study, fasting triglyceride level >4.5 mmol/L, serum creatinine >134 micromol/L (men) or >109 micromol/L (women)

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Roden, 2013[139] Multi-continent No	2010 2012 24 Wks	Yes	Not Extracted	Yes	NR/ 899 Inpatient/hospital Outpatient: primary care Outpatient: subspecialty care setting academic medical ctrs, hospitals, and private practices	Age <18, <20 in Japan, <18 or >65 in India, HbA1c >10% or 9% in Germany, <7%, BMI >45 kg/m2, Any kidney disease, diabetes treatment in 12 wks before randomization, uncontrolled hyperglycaemia (glucose concentration >13┬╖3 mmol/L after an overnight fast during the placebo run-in phase and confi rmed by a second measurement),, contraindications to sitagliptin according to the local label,, treatment with antiobesity drugs within 3 months before informed consent, treatment with systemic steroids at time of informed consent, change in dose of thyroid hormones within 6 wks before informed consent,, any uncontrolled endocrine disorder apart from type 2 diabetes., did not meet inclusion criteria after placebo run-in
Rosenstock, 2006[140] Multi-continent Not extracted	Start year 2003 to 2004 32 Wks	Yes	< 6 months	Yes	1252/468 multicenter	Age <18 or >70 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >11%, FPG >15 mmol/l, hematological disease, uncontrolled hypertension while on antihypertensive treatment, intermittent or chronic use of oral or intravenous corticosteroids, investigators discretion, use of investigational agent within 30 days of the study (or five half lives of the investigational drug if longer than 30 days), previous history of severe edema or medically serious fluid related event associated with TZD, acute or chronic metabolic acidosis, history of diabetic ketoacidosis

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rosenstock, 2010[141] Country NR NCT00482729	Neither year reported 26 Wks	Yes	Not Extracted	Yes	NR/ 655 NR	Age <18 or >80 yrs, HbA1c >11% or <7.50%, BMI <23 or >45 kg/m2, not drug-naive (current antihyperglycemmic medication or >6 days of any such agent within 3 months of screening), successful glycemic control with diet and exercise for >=2 months prior to screening
Rosenstock, 2012[142] Multi-continent NCT00327015	Neither year reported 12 Wks	No	Not Extracted	Yes	NR/ 451 NR	Age <18, >65 yrs, HbA1c >10.50% or <7%, unstable weight or BMI <25 or >45 kg/m^2 (<24 or >45 kg/m^2 for Asians), Diagnosed with type 2 diabetes for less than 3 months, On metformin monotherapy dose <1500mg/day, On metformin monotherapy for less than 3 months, Serum creatinine >1.5mg/dl for men and >1.4 mg/dl for women
Rosenstock, 2013[143] Multi-continent NCT00434954	Neither year reported 52 Wks	Yes	Not Extracted	Yes	NR/ 441 NR	Age <65 or >90 yrs, HbA1c >9.0% for patients on diet and exercise therapy alone,>8.0% for patients on oral antidiabetic monotherapy & >9.0% after washout period without medications within 2 wks or < 6.50%, not able or unwilling to self-monitor blood glucose with a home glucose monitor
Rosenstock, 2013[144] Multi-continent No	Neither year reported 12 Wks	Yes	Not Extracted	Yes	NR/ 495 NR	Age <18 or >80 yrs, HbA1c >9% if on metformin and one other OAD or >10 if on metformin monotherapy or <6.5% if on metformin and one other OAD, <7 if on MFM monotherapy, BMI >40 kg/m2, Any liver disease, Any kidney disease, prior treatment that didn't include MFM and one other oral OAD, unchanged antidiabetic therapy for <10 wks prior to screening including stable metformin therapy (ГёÑ1500 mg/day or maximum tolerated dose);, diseases of the central nervous system; chronic or clinically relevant acute infections; history of clinically relevant allergy/hypersensitivity;, treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months., h/o of MI, CVA, or TIA in past 6 mo, HbA1c <7 or >10 at start of placebo run-in, history of clinically relevant allergy/hypersensitivity, treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Rosenstock, 2015[145] Multi-continent NCT01606007	2012 2014 24 wks	Yes	Not extracted	Yes	NR/534 NR	No type 2 diabetes. On stable metformin therapy (>/=1,500 mg/day) for >=8 weeks before screening. Have Cpeptide concentrations >/=1.0 ng/mL. Uncontrolled hypertension (systolic blood pressure >/=160 mmHg and diastolic blood pressure >/=100 mmHg) at randomization. Fasting plasma glucose (FPG) >/=270 mg/dL during the 4-week lead-in period. Cardiovascular disease within 3 months of screening, congestive heart failure (New York Heart Association functional class IV). Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 or serum creatinine >/=1.5 mg/dL in men or >/=1.4 mg/dL in women. Patients who received any antidiabetic medication, other than metformin, for more than 14 days during the 12 weeks before screening.
Ross, 2012[146] Multi-continent NCTC00294723	2009 2010 12 Wks	Yes	Not Extracted	Yes	NR/ 491 NR	Age <18 or > 80 yrs, HbA1c >10.0% when taking met alone; 9.5% when taking met and no more than one other oral antidiabetic drug (SU, meglitinide, DPP-4 inhibitor or a-glucosidase inhibitor with unchanged dose for 12 wks prior to informed consent); 10% after the placebo run-in for or HbA1c < 7.00%, BMI > 45kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, total daily dosage of met was not >=1500mg/day or maximum tolerated dose b.i.d., or was on unstable dose (changed within 12 wks prior to randomisation or during the study), treatment within the prevous 3 months with a thiazolidinedione, a GLP-1 receptor agonist, or an antiobesity drug, major cvd event in last 6 months
Russell-Jones, 2012[147] Multi-continent NCT00701090	2008 2010 36 Wks	No	Not Extracted	Yes	NR/ 820 NR	Adults, HbA1c >11% or <7.1%, BMI <23 - >45 kg/m2, Prior use of any diabetes treatment, unstable weight
Schernthaner, 2015[148] Multi-continent NCT01006603	2009 2012 52 wks	Yes	NR	Yes	NR/720 NR	Age <65, HbA1c>9, HbA1c7, any liver disease, any kidney disease, type 1 diabetes, any antihyperglycaemic therapy other than metformin <8 wks before enrollment, glucocorticoids, cytochrome P450 3A4 inducers, history of ketoacidosis or hyperosmolar non-ketonic coma, haemoglobinopathies, cognitive function problems, alcohol or illegal drug abuse

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Schernthaner, 2004[149] Europe Not extracted	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Age <35 or >75 yrs, treatment experienced, HbA1c <7.5% or >11%, no Type 2 DM
Schondorf, 2011[150] Germany No	Neither year reported 24 Wks	No	Not Extracted	Yes	NR/ 46 NR	HbA1c >9.00% or <6.50%, Prior or current use of insulin, Any liver disease, Any kidney disease, not treated with metformin monotherapy in a maximal individually tolerated dose of 850 to 2000 mg, no dyslipidemia, significant cardiovascular disorder (NYHA I-IV), previous treatment with other oral antidiabetes drugs in addition to metformin
Schumm-Draeger, 2015[151] Multi-continent	2010 2011 NR	Yes	Not extracted	Yes	NR/400 NR	Not on stable dose of MET >=1500mg/day for >= 10 weeks. Weight loss (sx of uncontrolled dm). BP>=160/100. Clinically significant haematological or oncological conditions. Symptoms of poorly-controlled diabetes.
Scott, 2007[152] US Not extracted	Neither year reported 12 Wks	Run-in period but number excluded was NR	< 6 months	Yes	2186/743 NR	Age <21 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), Type 1 DM, gall bladder disease, elevated CK
Scott, 2008[153] Multi-continent Not extracted	Neither year reported 18 Wks	Run-in period but number excluded was NR	< 6 months	Yes	486/273 NR	Age <18 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >11%, not on 10 wks on stable dose of metformin, insulin use, Type 1 DM, glucose >270 mg/dL

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Seck, 2010[154] NR Not extracted	Neither year reported 2 years	Run-in period but number excluded was NR	< 6 months	Yes	2141/1172 NR	Age <17 or >78 yrs
Seino, 2010[155] Japan Not extracted	Neither year reported 24 wks	Yes	< 6 months	Yes	NR/464 NR	Age <20 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, HbA1c <7% or >10%, BMI >35 kg/m^2, treated with insulin within 12 wks of the start of the study, receiving or expecting to receive systemic corticosteroids, known hypoglycemia unawareness or recurrent major hypoglycemia unawareness or recurrent major hypoglycemia, no Type 2 DM, treated with diet therapy for less than 8 wks, on more than 1/2 of the recommended maximum dose of an SU (e.g., on more than 2.5 mg of glibenclamide)
Seino, 2012[156] Japan No	2008 2009 12 Wks	Yes	Not Extracted	Yes	NR/ 288 outpatient, but not specified	Age <20 or >=65 yrs, HbA1c >=10.4% after 8 wks of observation or <6.9% after 8 wks of observation, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, >=10% variation in A1c between week 4 and 8, not receiving metformin at a stable dosage for at least 12 wks plus specific dietary and exercise therapies, administration of any investigational drug, orhter than met, within 12 wks of study initiation, a history/symptoms of lactic acidosis, h/o drug abuse/dependency, severe cardiovascular or pulmonary function impairment or severe pancreatic, cerebrovascular, or hematologic diseases, dehydration, GI disorders, malignant tumours, elevated blood pressure (>=180 / 110mmHg
Shihara, 2011[157] Japan NCT00575588	2007 2010 6 Months	No	Not Extracted	No	NR/ 191 NR	Age <30 - >75 yrs, HbA1c >=10.4% or <6.9%, Prior or current use of study drug, Any liver disease, Any kidney disease, History of CVD, CHF, Any hematological condition, Any pancreas condition, not committed to stable diet & exercise regimen, use of any dim med in past month, capable of reading consent form

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Srivastava, 2012[158] India NCT00641056	2008 2009 18 Wks	No	Not Extracted	NR	NR/ 50 Outpatient (not specified if PC or subsp)	Age <=18 yrs, HbA1c >=10% or <=7%, Any liver disease, Any kidney disease, History of CVD, not on metformin monotherapy for at least 3 mo, type 1 diabetes, other terminal illness
St John Sutton, 2002[159] US Not extracted	Not extracted 52 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other
Stewart, 2006[160] Multinational Europe Not extracted	Start year 2003 to 2004 32 Wks	Yes	< 6 months	Yes	1397/526 NR	Age < 18 or > 70 yrs, history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or >9%, drug naive patients with FPG <7 mmol/l or >9 mmol/l, patient on monotherapy with FPG <6.0 mmol/l or >8 mmol/l, prior history of exposure to TZDs within previous 6 months, use of insulin anytime in the past, uncontrolled hypertension
Suzuki, 2014[161] Japan Not extracted	2009 2012 6 months	No	Not extracted	No	NR/534 Outpatient: subspecialty care setting	Type 1 diabetes. Severe complication of diabetes. Severe renal and liver dysfunction. Pregnant or nursing women and those who might be pregnant. Alcoholism. A history of stroke and cardiovascular events. Any patient whom the investigator judged to be inappropriate for this study.
Tan, 2004[162] Denmark, Finland, Norway, and Sweden Not extracted	Not extracted 52 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Treatment experienced, HbA1c <7.5% or >11% for patients not receiving ODM, <7.5 or >9.5 for patients receiving ODM, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Tan, 2004[163] Mexico Not extracted	Not extracted NR	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% or >11% in patients who were not receiving ODMs, and <7.5 or >9.5 in patients who were receiving ODM monotherapy, no Type 2 DM, other
Taskinen, 2011[164] Multi-continent NCT00637273	Neither year reported 24 Wks	Yes	Not Extracted	Yes	NR/ 701 NR	Age <18 or >80 yrs, HbA1c < 10.0% for metformin monotherapy patients, 9.0% for patients treated with an additional medication; by the start of the placebo run-in, 10.0% for all patients or HbA1c < 7.0% for met mono patients, 6.5% for patients treated with an additional medication; by the start of the placebo run-in, 7.0% for all patients, BMI >40 kg/m2, Any liver disease, Any kidney disease, not receiving met at a dose of >=1500mg/day (or max tolerated dose), more than one other oral antidiabetes medication, antidiabetes medications have changed within 10 wks prior to the date of informed consent or the dose of met was not stable for >=12 wks before randomization, treated with rosiglitazone, pioglitazone, a GLP-1 analogue, insulin or antiobesity drug within 3 months, changed dosage of thyroid hormone treatment within 6 wks or were being treated with systemic steroids at the date of informed consent, acute or chronic metabolic acidosis, hereditary galactose intolerance, dehydration, have participated in another trial of an investigational drug within the previous 2 months, acute MI, stroke, or TIA within last 6 months or acute or unstable CHF
Taslimi, 2013[165] Iran NCT00103857	2011 2011 3 Months	No	Not Extracted	No	NR/ 60 NR	HbA1c <7%, Prior use of any diabetes treatment, Prior or current use of study drug, Any liver disease, Any kidney disease, Pregnant, Diabetes diagnosed before the age of 30, congestive heart failure
Teramoto, 2007[166] Japan Not extracted	Neither year reported 24 Wks	Yes	NR	No	126/92 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), any medication affecting glucose metabolism, history of diabetic ketoacidosis, history of diabetic coma or pre-coma, Cushing's syndrome, history of allergy to thiazolizinediones, tumor therapy, receiving insulin for severe infection

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Tosi, 2003[167]*	Not extracted	Not extracted	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.3%, no Type 2 DM, other
Italy Not extracted	6 months (planned duration)					
Turkmen Kemal, 2007[168]	Start year 2005	No run-in period	< 6 months	NR	46/46	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), patient on diuretics, uncontrolled hypertension
Turkey	6 Months				Outpatient subspecialty care setting	
Not extracted						
Turner, 1999[169]	Start year 1977 End year 1991	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	NR/4075	Age <25 or >65 yrs, FPG<6 mmol/l x 2, individuals on diet only therapy who maintained their blood sugars <6 mmol/l on followup visits
United Kingdom					23 UKPDS centers	
Not extracted	9 Years					
Umpierrez, 2006[170]	Neither year reported	Run-in period but number excluded was NR	< 6 months	Yes	538/210	Age <18 or >79 yrs, HbA1c <7.5% and >10%, BMI <24 kg/m^2, diagnosis of Type 2 DM <6 months, no taking stable doses of metformin (1-2.5g/day) or extended-release metformin (0.5 -2.0g/day) as their only ODM for at least 2months prior to the study, C-peptide <0.27nmol/L, subjects treated with insulin, TZDs or SU within 3months prior to study enrollment, history of substance abuse, severe hypoglycemia, acute metabolic complications, clinically significant abnormal baseline laboratory values including hematology, blood chemistry or urinalysis
US					Outpatient primary care, Outpatient subspecialty care setting	
Not extracted	28 Wks					

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Umpierrez, 2014[171] Multi-continent No	2010 2012 52 Wks	Yes	Not Extracted	Yes	NR/ NR	Age <18 yrs, HbA1c >9.50% or <6.50%, Prior or current use of insulin, Prior or current use of study drug, on more than one oral antihyperglycemic medication(OAM) or on one OAM for <3 months prior to screening., receiving an OAM and taking >50% of the approved maximum daily dose per respective labels in participating countries, have been taking thiazolidinediones or GLP-1 receptor agonists during the 3 months prior to screening, on one oral medication < 3 months
van der Meer, 2009[172] Netherlands Not extracted	Neither year reported 24 Wks	Fewer than 10% of participants were excluded during run-in	< 6 months	Yes	173/80 NR	Age <45 or >65 yrs, female, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >8.5%, BMI <25 kg/m^2 or >32 kg/m^2, SBP <150 mmHg, DBP <85 mmHg, prior TZD or insulin use
Wang, 2015[173] China-Philipphines-Malaysia	2010 2012 24 wks	Yes	NR	Yes	NR/306 NR	Age <18 & >80, HbA1c>10, HbA1c7, BMI>45, prior or current use of insulin, prior or current use of study drug, any liver disease, any kidney disease, history of CVD, confirmed hyperglycemia (glucose 240 mg/dL after overnight fast during wash-out or run-in), current treatment with a TZD, insulin, GLP-1 agonist, DPP-4 inhibitor, or antiobesity drug, alcohol or drug abuse, steroids use
Weissman, 2005[174] US Not extracted	Not extracted 24 wks (planned duration)	Not extracted	Not extracted	Yes	Not extracted	Age <18 or >75 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <6.5% or >8.5% for patients having received prior combination treatment, HbA1c <7% or >10% prior monotherapy or drug naive patients, no Type 2 DM, other
White, 2014[175] Multi-continent NCT00885378	2009 2010 12 Wks	Yes	Not Extracted	Yes	NR/ 160 outpatient	Age <18 and >78 yrs, HbA1c >10% or <7%, BMI >45, Pregnant, Nursing, not on metformin monotherapy at >=1500 mg for >=8 wks prior to study start, marked polydipsia and polyuria and >10% weight loss<3 months before screening, h/o DKA or HHNC or insulin use in the last year, h/o CVD within 3 months of screening, CHF class 3 or 4 or known EF<=40%, h/o hemoglobinopathies

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Williams-Herman, 2009[176] NR Not extracted	Neither year reported 54 Wks	Run-in period but number excluded was NR	NR	Yes	3544/1091 NR	Age <18 or >78 yrs, HbA1c <7.5% or >11% after screening diet/exercise run-in (which included a wash-out period), lack of adequate compliance (>=75% by tablet count) during 2-week single-blind placebo run-in period, no Type 2 DM
Williams-Herman, 2010[177] Multi-continent No	Neither year reported 104 Wks	Yes	Not Extracted	Yes	NR/ 1091 NR	Age <18 or >78 yrs, HbA1c >11% or <7.50%, Any liver disease, Any kidney disease, History of CVD, completed the 54-week base study, >/= 75% compliant in taking study medication, had not developed contraindication to study medication
Xu, 2015[178] China NCT01147627	2010 2012 6 months	No	Not Extracted	No	NR/416 NR	Acute or severe chronic diabetic complications or illnesses (ketoacidosis, hyperosmotic state, lactic acidosis, severe microand macro-vascular complications, and hepatic dysfunction). Presence of glutamic acid decarboxylase antibodies. Use of drugs affecting gastrointestinal motility, weight and glycaemia. History of pancreatitis. Triglyceride (TG) levels ГёÑ5 mmolL-1. Body weight not atble over the last 3 months.
Yamanouchi, 2005[179] Japan Not extracted	Not extracted 12 months (planned duration)	Not extracted	Not extracted	NR	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, retinopathy, HbA1c <7.0%, no Type 2 DM, other

Author, year Country Registered protocol	Enrollment period Follow-up duration	Run-in period	Planned interval of follow-up	Pharma ceutical support	Number screened/ enrolled Source population	Exclusion criteria
Yang, 2011[180] Multinational Asia (China - India – SouthKorea No	Neither year reported 24 Wks	Yes	Not Extracted	Yes	NR/ 570 NR	Age <18 yrs, HbA1c >10% or <7%, Any liver disease, Any kidney disease, Pregnant, Nursing, not on stable dose of metformin; C-peptide <0.33 nmol/l, history of diabetic ketoacidosis or hyperosmolar coma, symptoms of poorly controlled dm, CHF - NYHA III-IV, use of sysetmic steroids or CYP 3A4 inducersHemoglobinopathies, signiifcant cardiovasc illness within 6 mo of enrollment, autoimmune skin d/o, GI surgery that could affect absorpotion, immunocompromised, drug or alcohol abuse in past 12 mo, abnormal lab, exam, ECG that would compromise safe, successful participation - investigator discretion, insulin in past year, Prior use of any diabetes treatment besides metformin within 8 wks, ever used DPP4 inhibitor
Yang, 2011[181] Asia - Korea, China, India No	Neither year reported 16 Wks	Yes	Not Extracted	Yes	NR/ 929 NR	Age <18 and >80 yrs, HbA1c >11% for subjects on OAD monotherapy and 10% for subjects on OAD combination therapy or <7%, BMI >45kg/m2, not treated with one or more oral antidiabetic drugs (OADs) for at least 3 months, treated with insulin within the last 3 months, after run-in with up-titration of metformin to 2000 mg/day and 3-wk maint at that dose, subj with FG 7-12.8 mmol/l could be randomized
Yang, 2012[182] China No	2009 2010 24 Wks	Yes	Not Extracted	Yes	NR/ 395 NR	Age <18 - >78 yrs, HbA1c >11% or 7.5%, Any liver disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing
Yoon, 2011[183] Korea NCT00097500	2007 2008 48 Wks	Yes	Not Extracted	Yes	NR/ 349 NR	Age <30 - >65 yrs, HbA1c >9.5% or <6.5%, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant
Yuan, 2012[184] China No	Neither year reported 26 Wks	No	Not Extracted	NR	NR/ 59 NR	Age <=18 yrs, HbA1c >10% or <7%, BMI <=28or >=40kg/m2, >=1months, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density

lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not Reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table D2. Population characteristics of studies evaluating diabetes medications for intermediate outcomes

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Seino, 2010[155]	Glibenclamide, 132	58.5	65	Asian: 100	24.4 NR	8.978	8.5	12
	Liraglutide, 268	58.2	68	NR	24.5 NR	8.92	8.1	22
DeFronzo, 2005[28]	Metformin + placebo, 113	54	NR	NR	34 100	8.2	6.6	NR
	Metformin + exenatide, 110	53	NR	NR	34 100	8.3	6.2	Nr
	Metformin + exenatide, 113	52	NR	NR	34 101	8.2	4.9	NR
Rosenstock, 2015[145]	Metformin + saxagliptin + placebo, 176	55	NR	NR	31.8 NR	9.03	8.2	NR
	Metformin + dapagliflozin + placebo, 179	54	NR	NR	31.5 NR	8.87	7.4	NR
Suzuki, 2014[161]	Sitagliptin, NR	56.1	56	NR	NR 81.7	9.1	1.9	NR
	Liraglutide, NR	58.6	62	NR	NR 82.3	9.8	2.4	NR
Xu, 2015[178]	Pioglitazone, 136	NR	55.1	NR	NR 70.6	8	NR	18
	Exenatide, 142	NR	67.3	NR	NR 71.7	8	NR	32
Del Prato, 2014[33]	Metformin + glipizide, 874	55.4	50.5	Caucasian: 61 African American: 9.3 Asian: 23.2 Other: 6.5	31.1 85.6	7.6	5.5	NR
	Metformin + alogliptin, 880	55.2	47.6	Caucasian: 63.3 African American: 8.4 Asian: 21.7 Other: 6.5	31.3 85.3	7.6	5.7	Nr

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + alogliptin, 885	55.5	51.1	Caucasian: 62.7 African American: 7.5 Asian: 23.4 Other: 6.4	31.3 86.3	7.6	5.4	NR
Schumm-Draeger, 2015[151]	Metformin + placebo, 101	58.5	46.5	NR	31.74 NR	7.94	5.53	7.9
	Metformin + dapagliflozin, 100	55.3	46.5	NR	33.09 NR	7.78	5.12	6
	Metformin + dapagliflozin, 99	58.5	49.5	NR	32.25 NR	7.71	5.45	9.1
Esteghamati, 2015[30]	Metformin, 42	49.4	40	NR	29.86 78.50	8.4	NR	2
	Metformin + pioglitazone, 42	51.83	45	NR	29.38 75.36	8.06	NR	0
Del Prato, 2015[32]	Metformin + glipizide, 401	58.6	54.9	NR	NR 87.6	7.74	6.6	NR
	Metformin + dapagliflozin, 400	58.1	55.3	NR	NR 88.4	7.69	6.1	NR
Derosa, 2010[39]	Metformin + glibenclamide, 65	NR	51	NR	28.5 NR	8.9	NR	8
	Metformin + exenatide, 45	NR	67	NR	28.7 NR	8.8	NR	4
DeFronzo, 2010[30]	Metformin + rosiglitazone, 45	NR	NR	NR	NR NR	7.9	NR	11
	Metformin + exenatide, 45	NR	NR	NR	NR NR	7.8	NR	12
Aschner, 2010[7]	Metformin, 439	55.7	44	NR	30.9 NR	7.2	2.1	75
	Sitagliptin, 455	56.3	48	NR	30.7 NR	7.2	2.6	61
Seck, 2010[154]	Metformin + sitagliptin, 248	57.6	57.3	AA: 3.6, Asian: 9.3, C: 77.4, H: 5.6, Other: 4	30.9 NR	7.3	5.8	231

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + glipizide, 584	57	62.9	AA: 5.1, Asian: 8.2, C: 78.5, H: 5.1, Other: 3.1	31.3 NR	7.3	5.7	328
Pratley, 2010[130]	Metformin + sitagliptin, 219	55	55	AA: 5, Asian: 1, C: 91, H: 16, Other: 4	32.6 93.1 kg	8.5	6.3	25
	Metformin + liraglutide, 221	55.9	52	AA: 10, Asian: 3, C: 82, H: 17, Other: 5	32.6 93.7 kg	8.4	6	27
	Metformin + liraglutide, 221	55	52	AA: 7, Asian: 2, C: 87, H: 15, Other: 4	33.1 94.6 kg	8.4	6.4	52
Home, 2009[89]	Metformin + rosiglitazone, 1117	57	53.8	C: 98.9	NR 93.5kg	7.8	6.1	NR
	Metformin + sulfonylurea, 1105	57.2	52.9	C: 98.4	NR 93.3 kg	7.8	6.3	NR
	Metformin + sulfonylurea, 1122	59.7	50.6	C: 99.1	NR 84.3kg	8	7.9	NR
	Metformin + sulfonylurea, 2227	58.5	51.7	C: 98.7	31.5 NR	7.9	7.1	233
	Rosiglitazone, 2220	58.4	51.4	C: 99.1	31.6 NR	7.9	7	218
	Rosiglitazone + sulfonylurea, 1103	59.8	49	NR	30.3 85.0kg	8	7.9	NR
Derosa, 2009[38]	Metformin, 67	55 (50 to 60)	51	C: 100	27.2 77.7 kg	9.1	NR	7
	Metformin + glimepiride, 66	57.7 (51.7-64.7)	48	C: 100	27.1 77.4 kg	9	NR	6
	Metformin + pioglitazone, 69	57 (50 to 64)	49	C: 100	27.4 76.4 kg	9.3	NR	9
	Pioglitazone, 69	54 (48 to 60)	46	C: 100	27.5 76.7 kg	9.2	NR	9
van der Meer, 2009[172]	Metformin + glimepiride, 39	56.4	100	NR	29.3 NR	7	3	2
	Pioglitazone + glimepiride, 39	56.8	100	NR	28.2 NR	7.1	4	5
Kaku, 2009[98]	Metformin, 86	53	57	NR	25.4 NR	7.55	5.6	7

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + pioglitazone, 83	52	66	NR	25.6 NR	7.58	4.5	9
Gupta, 2009[74]	Metformin, 17	56.9	37.5	C: 62.5	36.4 97.8 kg	6.0	NR	1
	Pioglitazone, 16	59.2	25	C: 78.5	35.7 98.5 kg	6.2	NR	2
	Pioglitazone, 18	55.7	33	C: 50	34.3 95.3 kg	6.4	NR	0
Williams-Herman, 2009[176]	Metformin, 182	54.2	45	NR	32 NR	8.5	4.1	46
	Metformin, 182	53.7	48	NR	32 NR	8.7	4.1	56
	Metformin + sitagliptin, 182	53.6	41	NR	32 NR	8.7	4.6	41
	Metformin + sitagliptin, 190	53.7	53	NR	32 NR	8.8	4.1	42
	Sitagliptin, 179	53.5	52	NR	31 NR	8.7	3.9	57
Kiyici, 2009[104]	Metformin, 16	52.4	NR	NR	31.6 NR	6.7	NR	NR
	Rosiglitazone, 19	50.7	NR	NR	31.2 NR	7.1	NR	NR
Jonker, 2009[94]	Metformin + glimepiride, 39	56.4	100	NR	29.1 NR	7	NR	NR
	Pioglitazone + glimepiride, 39	56.8	100	NR	28 NR	7.1	NR	NR
Perez, 2009[125]	Metformin, 210	53.7	46.7	AA: 6.7, Asian: 2.4, C: 88.1, H: 26.2	30.8 NR	8.65	NR	68
	Metformin + pioglitazone, 201	54.7	44.8	AA: 6, Asian: 1.5, C: 91.5, H: 24.4	30.8 NR	8.89	NR	44
	Pioglitazone, 189	54	34.9	AA: 6.9, Asian: 2.6, C: 87.3, H: 25.9	31.2 NR	8.69	NR	64
Rigby, 2009[137]	Metformin + rosiglitazone, 56	54.7	41	AA: 3.6, Asian: 0, C: 28.6, H: 67.9	NR 81.1 kg	8.06	7.57	5

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + sitagliptin, 56	54.8	35.7	AA: 1.8, Asian: 0, C: 23.2, H: 73.2	NR 79.6 kg	8.17	8.35	11
Jadzinsky, 2009[91]	Metformin + saxagliptin, 320	52.4	51.6	AA: 2.2, Asian: 15.9, C: 76.9, Other: 5	29.9 NR	9.4	2	58
	Metformin + saxagliptin, 323	52.1	45.2	AA: 2.2, Asian: 16.7, C: 75.2, Other: 5.9	30.3 NR	9.5	1.4	62
	Metformin, 328	51.8	49.7	AA: 1.2, Asian: 15.9, C: 76.5, Other: 6.4	30.2 NR	9.4	1.7	85
	Saxagliptin, 335	52	50.4	AA: 1.8, Asian: 16.7, C: 76.1, Other: 5.4	30.2 NR	9.6	1.7	110
DeFronzo, 2009[29]	Metformin + saxagliptin, 192	54.7	43.2	AA: 3.9, Asian: 4.2, C: 79.7, Other: 12	31.7 NR	8.1	6.7	44
	Metformin + saxagliptin, 191	54.7	53.9	AA: 5.8, Asian: 1.6, C: 83.2, Other: 9.4	31.2 NR	8.1	6.4	48
	Metformin + saxagliptin, 181	54.2	52.5	AA: 7.7, Asian: 2.8, C: 79.6, Other: 9.9	31.1 NR	8.0	6.3	41
	Metformin, 179	54.8	53.6	AA: 3.9, Asian: 2.2, C: 83.8, Other: 10.1	31.6 NR	8.1	6.7	40
Garber, 2009[66]	Glimepiride, 248	53.4	54	AA: 12, Asian: 4, C: 77, H: 38, Other: 7	33.2 93.4 kg	8.4	5.6	96
	Liraglutide, 247	52	49	AA: 12, Asian: 6, C: 75, H: 35, Other: 7	32.8 92.8 kg	8.3	5.3	74
Kato, 2009[100]	Liraglutide, 251	53.7	47	AA: 14, Asian: 2, C: 80, H: 32, Other: 5	32.3 92.5 kg	8.3	5.2	89
	Metformin, 25	58.6	56	NR	27.5 NR	7.1	NR	NR
	Pioglitazone, 25	51.4	48	NR	28.4 NR	7.4	NR	NR
Erdem, 2008[46]	Metformin, 27	55.09	33	NR	31.41 NR	6.74	NR	4
	Pioglitazone, 26	54.9	31	NR	30.41 NR	6.34	NR	5

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Iliadis, 2007[90]	Metformin, 16	57.8	NR	NR	30.8 80.8 kg	7.8	20.9 months	1
	Rosiglitazone, 16	56.3	NR	NR	31 83.2 kg	7.2	30.7 months	2
Scott, 2008[153]	Metformin, 92	55.3	59	Asian: 39, C: 61	30 84.6 kg	7.7	5.4	9
	Metformin + rosiglitazone, 87	54.8	63	Asian: 38, C: 59, Others: 3	30.4 84.9 kg	7.7	4.6	2
Robbins, 2007[138]	Metformin + sitagliptin, 94	55.2	55	Asian: 38, C: 61, Others: 1	30.3 83.1 kg	7.8	4.9	9
	Metformin + glargine, 159	58.1	49.4	AA: 5.7, Asian: 14.6, C: 63.3, H: 16.4	32 88.1kg	7.8	12.5	22
	Metformin + insulin lispro 50/50, 158	57.4	50.3	AA: 5.7, Asian: 14, C: 65, H: 15.3	32.1 89.1kg	7.8	11.3	15
Hamann, 2008[80]	Metformin + rosiglitazone, 294	58.5	53	C: 94	33 91.4kg	8	6.3	61
	Metformin + sulfonylurea, 302	59.3	52	C: 95	32.2 88.9kg	8	6.4	71
Chien, 2007[24]	Glyburide, 25	63	53	NR	25.3 63.7 kg	8.69	8.6	6
	Metformin, 25	59	41	NR	25.7 65.6 kg	8.88	6.4	8
Turkmen Kemal, 2007[168]	Metformin + glyburide, 26	60	71	NR	24.2 63.8 kg	8.71	9	5
	Metformin + glyburide, 26	57	62	NR	24.2 61.3 kg	8.85	6.6	5
	Metformin, 16	56.8 (40 to 70)	25	NR	34.5 NR	6.3	1.5	0
	Rosiglitazone, 13	55.92 (42 to 68)	30	NR	30.8 75 kg	6.2	2.75	1
Comaschi, 2007[25]	Metformin + pioglitazone, 103	57	45.63	NR	32.2 85.8 kg	8.4	NR	27
	Metformin + sulfonylurea, 80	59.9	55	NR	29.9 81.9 kg	8.6	NR	13

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Home, 2007[88]	Pioglitazone + sulfonylurea, 67	62.2	56.72	NR	28.9 78.8 kg	8.7	NR	14
	Metformin + rosiglitazone, 259	57	54	NR	32.7 93kg	7.9	6.1	52
	Metformin + sulfonylurea, 265	57	52	NR	NR 91kg	7.8	7	22
Teramoto, 2007[166]	Metformin + sulfonylurea, 284	60	52	NR	NR 83kg	8	8.1	54
	Rosiglitazone + sulfonylurea, 311	61	49	NR	NR 84kg	8	7.9	74
	Glibenclamide, 46	56.4	76	NR	25.2 NR	8.36	NR	5
	Pioglitazone, 46	57	72	NR	24.7 NR	8.01	NR	7
Goldstein, 2007[72]	Metformin, 182	53.4	48.9	AA: 6.6, Asian: 7.7, C: 47.8, H: 30.2, not specified: 7.7	32.1 NR	8.9	4.5	29
	Metformin, 182	53.2	45.1	AA: 4.9, Asian: 5.5, C: 58.2, H: 21.4, not specified: 9.9	32.2 NR	8.7	4.4	182
Nauck, 2007[118]	Metformin + sitagliptin, 182	53.3	42.3	AA: 7.7, Asian: 6, C: 52.2, H: 26.9, not specified: 7.1	32.4 NR	8.7	4.4	18
	Metformin + sitagliptin, 190	54.1	55.3	AA: 6.8, Asian: 4.7, C: 53.7, H: 28.9, not specified: 5.8	32.1 NR	8.8	4.5	26
	Sitagliptin, 179	53.3	52	AA: 6.1, Asian: 3.4, C: 52, H: 29.1, not specified: 9.5	31.2 NR	8.9	4.4	37
	Metformin + glipizide, 584	56.6	61.3	AA: 6, Asian: 8.4, C: 74.3, H: 7.9, Other: 3.4	31.3 89.7 kg	7.6	6.2	172
	Metformin + sitagliptin, 588	56.8	57.1	AA: 7, Asian: 8.5, C: 73.5, H: 7.3, Other: 3.7	31.2 89.5 kg	7.7	6.5	202
Kim, 2007[102]	Metformin + glimepiride, 60	57.6	50	NR	25.8 66.7 kg	7.7	3.4	4
	Rosiglitazone + glimepiride, 60	56.5	52.63	NR	25.7 68.1 kg	8.1	3.5	3

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Raskin, 2007[134]	Metformin + aspart 70/30, 79	52	52	AA: 13, Asian: 3, C: 52, H: 32, Other: 1	31.2 88.7kg	9.9	NR	12
	Metformin + glargine, 78	51.7	54	AA: 15, Asian: 4, C: 47, H: 32, Other: 1	30.8 86.2kg	9.9	NR	6
Hanefeld, 2007[82]	Glibenclamide, 203	60.1	70	AA: 0, C: 99, Other: 1	28.7 NR	8.2	6.4	13
	Rosiglitazone, 189	60.6	58	AA: 0, C: 97, Other: 3	28.8 NR	8.2	6	9
Scott, 2007[152]	Rosiglitazone, 195	60.4	68	AA: 0, C: 8, Other: 2	28.7 NR	8.1	5.9	12
	Glipizide, 123	54.7 (21-76)	56.9	AA: 3.3, Asian: 4.9, C: 61, Other: 24.4, Multiracial: 6.5	30.6 NR	7.9	4.7	23
	Sitagliptin, 123	56.2 (34-75)	48	AA: 4.9, Asian: 4.9, C: 63.4, multiracial: 5.7, Other: 21.1	30.5 NR	7.9	4.9	7
Davies, 2007[26]	Sitagliptin, 123	55.6 (34-76)	57.7	AA: 8.9, Asian: 4.9, C: 61, Multiracial: 6.5, Other: 18.7	31.4 NR	7.9	5	15
	Sitagliptin, 124	55.1 (28 - 75)	52.4	AA: 4.8, Asian: 2.4, C: 69.4, Multiracial: 7.3, Other: 16.1	30.4 NR	7.8	4.2	12
	Sitagliptin, 125	55.1 (30 - 76)	49.6	AA: 6.4, Asian: 7 5.6, C: 68.8, multiracial: 6.4, Other: 12.8	30.8 NR	7.9	4.3	18
	Metformin + NPH, 29	57.9	48.28	AA: 0, Asian: 21, C: 66	32.6 90.4 kg	10	7.3	5
	Metformin + BHI 70/30, 27	57.4	80	AA: 4, Asian: 22, C: 70	30.2 82.2 kg	9	9.1	0
Kahn, 2006[97]	Glyburide, 1441	56.4	58	AA: 4.2, Asian: 2.2, C: 89, H: 4.2, Other: 0.3	32.2 92 kg	7.35	(<1: 44, 1-2: 52, >2: 4)	634
	Metformin, 1454	57.9	59.4	AA: 3.7, Asian: 2.4, C: 89.1, H: 3.8, Other: 1	32.1 91.6 kg	7.36	(<1: 46, 1-2: 50, >2: 4)	551
Charbonnel,	Rosiglitazone, 1456	56.3	55.7	AA: 4.2, Asian: 2.7, C: 87.2, H: 76 5.2, Other: 0.7	32.2 91.5 kg	7.36	(<1: 45, 1-2: 52, >2: 3)	539

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
2006[21]	Metformin, 237	54.7	59.5	AA: 5.9, Asian: 11, C: 67.1, H: 11.8, Other: 4.2	31.5 NR	(<8: 54, 8 -8.9: 30, ≥9: 15)	6.6	45
	Metformin + sitagliptin, 464	54.4	55.8	AA: 6.7, Asian: 10.6, C: 63.1, H: 15.5	30.9 NR	(<8: 55, 8 -8.9: 31, ≥9: 14)	6	48
Rosenstock, 2006[140]	Metformin, 154	51.5	56	AA: 5, Asian: 14, C: 58, H: 21, Other: <1	32.5 NR	8.8	2.9	31
	Metformin + rosiglitazone, 155	50.1	57	AA: 6, Asian: 12, C: 54, H: 26	33.2 NR	8.9	2.3	19
Jain, 2006[92]	Rosiglitazone, 159	50.6	58	AA: 5, Asian: 14, C: 59, H: 19, Other: 3	32.8 NR	8.8	2.7	22
	Glyburide, 251	52.1	56.2	AA: 13.5, Asian: 0, C: 65.7, H: 19.9, Native American: 0.4, Other: 0.4	32.8 94.3 kg	9.2	0.78	123
	Pioglitazone, 251	52.1	53	AA: 15.9, Asian: 1.6, C: 61, H: 20.7, 0ther: 0.4, Native American: 1 0.4	32.5 93.9 kg	9.2	0.8	117
Stewart, 2006[160]	Metformin, 272	59	56	AA: <1, Asian: <1, C: 99, H: <1, Native Hawaiian/Other Pacific Islander: <1	30.6 87.2 kg	7.2	3.7	54
	Metformin + rosiglitazone, 254	58.8	55	AA: 0, Asian: 1, C: 98, H: <1, Native Hawaiian /Other pacific islander: 0	30.9 88.1 kg	7.2	3.7	50
Bakris, 2006[12]	Metformin + glyburide, 185	58.8	69	C: 76	31.8 90.3 kg	8.3	7.6	5
	Metformin + rosiglitazone, 204	60	63	C: 78	31.6 89.2 kg	8.5	8	10
Umpierrez, 2006[170]	Metformin + glimepiride, 96	51.6	55.2	AA: 13.5, Asian: 1.0, C: 79.2, H: 5.2, Other: 1.0	34.54 NR	8.4	4.9	11
	Metformin + pioglitazone, 109	55.7	52.3	AA: 15.9, Asian: 3.7, C: 78.5, H: 1.9, Other: 0	33.81 NR	8.31	5.9	17

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Kvapil, 2006[105]	Metformin + aspart 70/30, 116	56.4	46	NR 11	30.4 85.1 kg	9.	6.7	11
	Metformin + glibenclamide, 114	58.1	46	NR	30.5 84.0 kg	9.4	8.1	5
Derosa, 2005[35]	Metformin + glimepiride, 49	52	47	NR	26.8 75.6 kg	7.9	4	2
	Metformin + rosiglitazone, 50	54	50	NR	26.6 74.2 kg	8.0	5	2
Derosa, 2005[36]	Metformin + glimepiride, 49	52	47	NR	26.8 NR	7.9	4	2
	Metformin + rosiglitazone, 50	54	50	NR	26.6 NR	8.0	5	2
Nakamura, 2004[116]	Glibenclamide, 15	55	53	NR	NR NR	7.8	19.2	0
	Pioglitazone, 15	57	60	NR	NR NR	7.9	17.5	NR
Malone, 2003[112]	Metformin + glibenclamide, 301	59	49	AA: 1, C: 89, H: 6, Other: 4	29.6 81.7 kg	9.27	7.4	29
	Metformin + lispro 75/25, 296	58	57	AA: 0.7, C: 88.9, H: 7.4, Other: 3	29.8 83.0 kg	9.17	8.0	25
Turner, 1999[169]	Any in the Sulfonylurea class, 1305	NR	NR	NR	NR NR	NR	NR	NR
	Metformin, 340	NR	NR	NR	NR NR	NR	NR	NR
Leiter, 2005[108]	Total, 4075	53	NR	AA: 9, Asian: 10, C: 81	29 NR	(median : 9.1)	NR	4 loss to followup
	Metformin, 78	60	56	C: 78, Other: 22	32.2 NR	7.5	5.7	13
	Metformin + rosiglitazone, 158	58	65	C: 76, Other: 24	33 NR	7.5	5.3	18
Garber, 2006[65]	Metformin + rosiglitazone, 158	56 (24 - 78)	65	AA: 6, C: 79, Asian: 3, H: 10, O: 3	32 94 kg	8.4	6	Not extracted
	Metformin + glibenclamide, 160	56 (31 - 78)	56	AA: 5, C: 80, Asian: 3, H: 11, O: 2	32 93 kg	8.5	5	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Nakamura, 2006[185]	Pioglitazone, 17	56	53	NR	NR NR	8	16	NR
	Glibenclamide, 18	53.5	56	NR	NR NR	7.8	16.5	NR
Weissman, 2005[174]	Metformin + rosiglitazone, 358	55.5	NR	NR	34.4 98.2 kg	8.05	NR	Not extracted
	Metformin, 351	55.7	NR	NR	33.8 96.7 kg	7.97	NR	Not extracted
Bailey, 2005[9]	Metformin + rosiglitazone, 288	58.1	58	AA: 1, C: 97, Asian: 1, H: 0, O: 1	32.2 90.9 kg	7.4	6	Not extracted
	Metformin, 280	57.6	57	AA: <1, C: 98, Asian: 1, H: 0, O: 1	32.1 89.5 kg	7.5	6.1	Not extracted
Yamanouchi, 2005[179]	Pioglitazone, 38	55.2	47	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.8 NR	10.2	3.2 months	Not extracted
	Glimepiride, 37	55.6	51	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.6 NR	9.8	3.3 months	Not extracted
Pfutzner, 2005[127]	Metformin, 39	54.7	20	AA: 0, C: 0, Asian: 0, H: 0, O: 100	26.2 NR	9.9	3 months	Not extracted
	Glimepiride, 84	63	61.9	AA: 0, C: 96.4, Asian: 0, H: 0, O: 3.7	31.8 NR	7.44	6.9	Not extracted
	Pioglitazone, 89	62.2	61.8	AA: 0, C: 98.8, Asian: 0, H: 0, O: 1.1	31.7 NR	7.52	7.4	Not extracted
Derosa, 2005[37]	Metformin + glimepiride, 47	52	49	NR	26.8 NR	7.9	4	Not extracted
	Metformin + rosiglitazone, 48	54	52	NR	26.6 NR	8	5	Not extracted
Feinglos, 2005[52]	Metformin + glipizide, 61	57.7 (30-80)	46	AA: 8.2, C: 78.7, Asian: 3.3, H: 8.2, O: 1.6	31.7 90 kg	7.45	6.5	Not extracted
	Metformin, 61	58.8 (40-81)	41	AA: 16.4, C: 68.9, Asian: 3.3, H: 8.2, O: 3.3	32.1 90.8 kg	7.64	4.6	Not extracted
Ramachandran, 2004[133]	Glimepiride, 18	45.3	50	AA: 0, C: 0, Asian: 0, H: 0, O: 100	24.6 65.7 kg	10.2	0	Not extracted
	Metformin, 21	44.4	71	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.7 67.7 kg	9.6	0	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Schernthaner, 2004[149]	Pioglitazone, 23	45.1	74	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.5 68.9 kg	9.3	0	Not extracted
	Metformin, 597	56	57.8	NR	31.4 89.7 kg	8.7	3.1	Not extracted
	Pioglitazone, 597	57	52.6	NR	31.2 88.2 kg	8.7	3.4	Not extracted
Derosa, 2004[34]	Glimepiride, 81	56	47	NR	27.6 NR	8.5	NR	Not extracted
	Metformin, 83	58	51	NR	28.1 NR	8.4	NR	Not extracted
Tan, 2004[162]	Glibenclamide, 109	57.9	73	AA: 0, C: 100, Asian: 0, H: 0, O: 0	29.6 89 kg	8.5	62.6 months	Not extracted
	Pioglitazone, 91	60	62	AA: 0, C: 99, Asian: 0, H: 0, O: 1	30.2 88.4 kg	8.4	57.1 months	Not extracted
Tan, 2004[163]	Glimepiride, 123	55.7	53	AA: 0, C: 1, Asian: 0, H: 99, O: 0	28.8 74.5 kg	8.45	81.2 months	Not extracted
	Pioglitazone, 121	55.1	45	AA: 0, C: 0, Asian: 0, H: 100, O: 0	29.3 74.2 kg	8.54	77.8 months	Not extracted
Natali, 2004[117]	Metformin, 28	58	79	NR	28 NR	7.8	6.3	Not extracted
	Rosiglitazone, 24	59	92	NR	27.6 NR	7.7	6.5	Not extracted
Hanefeld, 2004[81]	Metformin + unspecified Sulfonylurea, 320	60	54.7	AA: 0.9, C: 98.4, Asian: 0, H: 0, O: 0.6	30 84.9 kg	8.8	7.1	Not extracted
	Unspecified sulfonylurea + pioglitazone, 31	60	53.6	AA: 0.6, C: 99.4, Asian: 0, H: 0, O: 0	30.2 85.3 kg	8.82	7	Not extracted
Lawrence, 2004[107]	Metformin, 20	59.5	60	NR	(Median 29.2) NR	8.04	NR	Not extracted
	Pioglitazone, 20	60.4	70	NR	(Median 30.6) NR	7.43	NR	Not extracted
Madsbad,	Glimepiride, 27	57	59	NR	30.2 NR	7.8	3.8	0

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
2004[110]	Liraglutide, 26	53	85	NR	30.2 NR	7.4	4.1	3
Garber, 2003[64]	Liraglutide, 25	58	60	NR	32 NR	7.9	4.4	3
	Liraglutide, 27	57	67	NR	30.1 NR	7.7	4.5	7
	Liraglutide, 30	57	67	NR	30.4 NR	7.4	4.6	2
	Liraglutide, 29	58	55	NR	31.9 NR	7.4	6.1	2
	Glyburide, 151	55.3	43.7	AA: 7.3, C: 81.5, Asian: 0, H: 7.9, O: 3.3	31.1 91 kg	8.7	3	Not extracted
	Metformin + glyburide, 171	55.6	44	AA: 10.5, C: 77.2, Asian: 0, H: 8.8, O: 3.5	31.4 91.9 kg	8.8	3	Not extracted
Tosi, 2003[167]	Metformin, 164	54.7	43.3	AA: 6.7, C: 80.5, Asian: 0, H: 9.1, O: 3.7	31.4 92.8 kg	8.5	2.6	Not extracted
	Glibenclamide, 20	NR	NR	NR	NR NR	NR	NR	Not extracted
	Glibenclamide, 21	NR	NR	NR	NR NR	NR	NR	Not extracted
Goldstein, 2003[71]	Metformin + glibenclamide, 39	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin + glibenclamide, 41	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin, 19	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin, 20	NR	NR	NR	NR NR	NR	NR	Not extracted
	Glipizide, 84	57.4	64.3	AA: 11.9, C: 71.4, Asian: 2.4, H: 14.3, O: 0	30.6 89.9 kg	8.9	6.5	Not extracted
	Metformin + glipizide, 87	54.6	58.6	AA: 11.5, C: 72.4, Asian: 0, H: 16.1, O: 0	31.7 94 kg	8.7	5.9	Not extracted
Pavo, 2003[123]	Metformin, 76	56.6	61.8	AA: 15.8, C: 65.8, Asian: 1.3, H: 17.1, O: 0	31.6 93.8 kg	8.7	7.3	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin, 100	55.8	56	NR	31.1 88.9 kg	8.6	0.53	Not extracted
	Pioglitazone, 105	54.2	43.8	NR	31.3 86.6 kg	8.6	0.47	Not extracted
Bakris, 2003[11]	Rosiglitazone, 57	5.1	75	NR	NR NR	9.1	NR	Not extracted
	Glyburide, 64	56.1	71	NR	NR NR	9.5	NR	Not extracted
Hallsten, 2002[79]	Metformin, 13	57.8	62	NR	29.9 NR	6.9	NR	Not extracted
	Rosiglitazone, 14	58.6	71	NR	29.3 NR	6.8	NR	Not extracted
Blonde, 2002[16]	Glyburide, 164	55.8	57.3	AA: 12.2, C: 66.5, Asian: 0, H: 17.1, O: 4.3	30.3 88 kg	9.64	7.01	Not extracted
	Metformin + glyburide, 160	55.4	55.6	AA: 12.5, C: 70, Asian: 0, H: 15.6, O: 1.9	30.7 89.4 kg	9.41	7.36	Not extracted
St John Sutton, 2002[159]	Metformin + glyburide, 162	55.6	63.6	AA: 9.3, C: 67.9, Asian: 0, H: 19.1, O: 3.7	30.6 89.6 kg	9.42	6.97	Not extracted
	Metformin, 153	57.6	62.1	AA: 10.5, C: 69.3, Asian: 0, H: 17, O: 3.3	30.6 89.5 kg	9.51	8.18	Not extracted
	Glyburide, 99	56.1 (40 - 76)	71	AA: 3, C: 76, Asian: 0, H: 0, O: 21	(BMI ≥27: 65.7) NR	9.5	6.2	Not extracted
	Rosiglitazone, 104	55.1 (40 - 77)	75	AA: 5, C: 73, Asian: 0, H: 0, O: 22	(BMI ≥27: 67.3) NR	9.1	5.3	Not extracted
Marre, 2002[113]	Glibenclamide, 103	58.7	55	NR	29.3 82.5 kg	7.88	6.6	Not extracted
	Metformin + glibenclamide, 101	58	50	NR	30.1 84.7 kg	7.89	5.9	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Garber, 2002[63]	Metformin + glibenclamide, 103	60.7	54	NR	29.7 83.1 kg	7.62	6.7	Not extracted
	Metformin, 104	57.5	60	NR	29.9 84.9 kg	8.09	5.4	Not extracted
	Glyburide, 161	56.5	50.9	AA: 9.3, C: 78.3, Asian: 0, H: 8.7, O: 3.7	30.3 87.2 kg	8.21	2.81	Not extracted
	Metformin + glyburide, 158	56.9	57.6	AA: 12.7, C: 74.1, Asian: 0, H: 11.4, O: 1.9	30.1 88.8 kg	8.25	3.52	Not extracted
Gomez-Perez, 2002[73]	Metformin + glyburide, 165	58.1	58.2	AA: 6.1, C: 79.4, Asian: 0, H: 9.7, O: 4.9	29.6 86.7 kg	8.18	3.3	Not extracted
	Metformin, 161	56	57.8	AA: 4.3, C: 80.7, Asian: 0, H: 12.4, O: 2.5	30.4 88.6 kg	8.26	2.98	Not extracted
	Metformin + rosiglitazone, 35	51.7 (40 - 73)	29	AA: 0, C: 0, Asian: 0, H: 80, O: 20	28 NR	NR	11.1	Not extracted
	Metformin + rosiglitazone, 36	54.2 (42 - 76)	19	AA: 0, C: 11, Asian: 0, H: 72, O: 17	27.6 NR	NR	10.7	Not extracted
Charpentier, 2001[22]	Metformin, 34	53.4 (40 - 68)	29	AA: 0, C: 3, Asian: 0, H: 76, O: 21	28.5 NR	NR	9.1	Not extracted
	Metformin + glimepiride, 147	56.8 (36 - 70)	59	NR	29.5 81.2 kg	6.4	5.6	Not extracted
	Glimepiride, 150	55.4 (35 - 70)	58	NR	29.3 81 kg	6.5	5.3	Not extracted
Amador-Licona, 2000[186]	Metformin, 75	56.7 (36 - 69)	60	NR	29.2 82.2 kg	6.8	7	Not extracted
	Glibenclamide, 23	48.2	30	NR	30.4 73.2 kg	8.4	4	Not extracted
	Metformin, 28	49.3	39	NR	26.8 70.7 kg	8.5	4.5	Not extracted
Einhorn, 2000[45]	Metformin + pioglitazone, 168	55.5	54.8	AA: 8.3, C: 81, Asian: 0, H: 10.1, O: 0.6	32.11 NR	9.86	NR	Not extracted
	Metformin, 160	55.7	60	AA: 6.3, C: 86.9, Asian: 0, H: 3.8, O: 3.1	32.12 NR	9.75	NR	Not extracted
Fonseca, 2000[55]	Metformin + rosiglitazone, 113	58.3	68.2	AA: 10, C: 77.3, Asian: 0, H: 0, O: 12.7	29.8 NR	8.9	8.3	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + rosiglitazone, 119	57.5	62.1	AA: 6.9, C: 80.2, Asian: 0, H: 0, O: 12.9	30.2 NR	8.9	7.5	Not extracted
Nakamura, 2000[115]	Metformin, 116	58.8	74.3	AA: 3.5, C: 81.4, Asian: 0, H: 0, O: 15	30.3 NR	8.6	7.3	Not extracted
	Glibenclamide, 15	61	53	NR	NR NR	7.8	14	Not extracted
	Pioglitazone, 15	60	47	NR	NR NR	7.7	16	Not extracted
DeFronzo, 1995[27]	Metformin + glyburide, 213	55	46	NR	29 92.1 kg	8.8	7.8	Not extracted
	Metformin, 143	53	43	NR	29.9 94.4 kg	8.4	6	Not extracted
Hermann, 1994[86]	Glyburide, 209	56	49	NR	29.1 92.6 kg	8.5	8.7	Not extracted
	Metformin, 210	55	46	NR	29.4 92.6 kg	8.9	8.4	Not extracted
	Glibenclamide, 21	NR	NR	NR	NR 82.6 kg	6.7	NR	Not extracted
	Metformin + glibenclamide, 13	NR	NR	NR	NR 84.6 kg	7.8	NR	Not extracted
Campbell, 1994[19]	Metformin + glibenclamide, 13	NR	NR	NR	NR 76 kg	7.8	NR	Not extracted
	Metformin + glibenclamide, 18	NR	NR	NR	NR 83.2 kg	8.4	NR	Not extracted
	Metformin + glibenclamide, 54	NR	NR	NR	NR 80.2 kg	6.8	NR	Not extracted
	Metformin, 25	60 (34 - 74)	NR	NR	NR 78.6 kg	6.9	4	Not extracted
	Glipizide, 24	57	33	NR	31.2 82.2 kg	11.8	2.8	Not extracted
	Metformin, 24	57	33	NR	29.6 78.2 kg	11.5	2.3	Not extracted
Hermann,	Metformin, 16	60 overall (38 - 73)	64 overall	NR	27 76.5 kg	6.7	NR	Not extracted

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
1991[85]	Glibenclamide, 17	60 overall (38 - 73)	64 overall	NR	29.2 84.1 kg	6.6	NR	Not extracted
Hermann, 1991[85]	Metformin + glibenclamide, 11	60 overall (38 - 73)	64 overall	NR	26.1 74.4 kg	7.8	NR	Not extracted
	Metformin + glibenclamide, 12	60 overall (38 - 73)	64 overall	NR	30 87.3 kg	7.7	NR	Not extracted
	Glibenclamide, 34	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin + glibenclamide, 72	60 (34 - 74)	79	NR	28.4 82.3 kg	NR	NR	Not extracted
Aaboe, 2010[1]	Metformin, 38	NR	NR	NR	NR NR	NR	NR	Not extracted
	Metformin + sitagliptin 12	39-64	67	NR	33.2 102 kg median	8 median	3.6 median	NR
	Metformin + placebo 12	31-72	75	NR	30.7 100 kg median	7.7 median	5.8 median	NR
Ahren, 2014[2]	Metformin + placebo 104	56.1	49.5	C: 63.4, AA: 22.8, Asian: 5, H: 31.7	32.8 91.6 kg	8.2	6.7	42
	Metformin + glimepiride + placebo, 317	54.4	51.5	C: 71.7, AA: 12.7, Asian: 5.2, H: 34.9	32.5 91.8 kg	8.1	6	99
Alba, 2013[3]	Metformin + sitagliptin + placebo, 313	54.3	46	C: 74.5, AA: 11.6, Asian: 6.6, H: 36.8	32.5 90.3 kg	8.1	5.8	101
	Metformin + albiglutide + placebo, 315	54.3	44.7	C: 70.9, AA: 17.5, Asian: 6, H: 32.8	32.7 89.6 kg	8.1	6	100
	Pioglitazone, 54	53.4	42.6	C: 79.6, AA: 16.7, Asian: 1.9, H: 38.9, O: 1.9	NR 86.6kg	7.9	2.4	2
	Sitagliptin, 52	54.6	53.8	C: 86.5, AA: 11.5, Asian: 1.9, H: 36.4	NR 85.7kg	7.7	2.4	6
Apovian, 2010[4]	Metformin, 51	55	39	NR	NR 94.9kg	7.2	3.9	26
	Metformin + exenatide, 52	53.4	29	NR	NR 91.4 kg	7.5	4.3	26

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Arechavaleta, 2011[5]	Metformin + glimepiride + placebo, 519	56.2	53.8	C: 57.4, AA: 1.2, Asian: 21.4, O: 20	NR 82 kg	NR	6.7	51
	Metformin + sitagliptin + placebo, 516	56.3	55	C: 57.6, AA: 1.2, Asian: 21.1, O: 20.1	NR 80.6 kg	NR	6.8	48
Arjona Ferreira, 2013[6]	Glipizide + placebo, 212	64.3	54.9	C: 28.2, AA: 1.4, Asian: 58.5, H: 28.9, O: 12	NR 70.2kg	7.8	10.1	NR
	Sitagliptin + placebo, 211	64.8	59.3	C: 29.6, AA: 1.5, Asian: 53.3, H: 33.3, O: 15.5	NR 68.0kg	7.8	10.7	NR
Aschner, 2012[8]	Metformin + sitagliptin, 265	53.3	52	NR	NR 84.2 kg	8.5	4.8	12
	Metformin + insulin glargine, 250	53.9	50	NR	NR 83.4 kg	8.5	3.9	23
Bailey, 2013[10]	Metformin + placebo, 137	53.7	55	NR	31.8 NR	8.11	5.8	64
	Metformin + dapagliflozin + placebo, 137	55	51	NR	31.6 NR	7.99	6	55
Barnett, 2012[13]	Metformin + dapagliflozin, 137	54.3	50	NR	31.4 NR	8.17	6.4	48
	Metformin + dapagliflozin + placebo, 135	52.7	57	NR	31.2 NR	7.92	6.1	40
	Glimepiride, 76	56.7	43.4	C: 67.1, Asian: 27.6, O: 5.3	NR 80.9 kg	8.1	NR	18
	Linagliptin, 151	56.4	36.4	C: 70.2, Asian: 27.8, O: 2	NR 77.0 kg	8.1	NR	32
Bergenstal, 2010[14]	Metformin + pioglitazone + placebo, 165	53	48	C: 39, AA: 8, Asian: 24, H: 27, O: 2	NR 88 kg	8.5	6	NR
	Metformin + sitagliptin + placebo, 166	52	52	C: 30, AA: 12, Asian: 25, H: 30, O: 3	NR 87 kg	8.5	5	NR
Bergenstal, 2012[15]	Metformin + exenatide + placebo, 160	52	56	C: 33, AA: 12, Asian: 23, H: 31, O: 1	32 89 kg	8.6	6	NR
	Metformin + placebo, 93	56.1	52	C: 77, AA: 6, Asian: 10, H: 11, O: 8	NR 91.1 kg	8.03	5.5	10
	Metformin + sitagliptin + placebo, 185	55.5	59	C: 76, AA: 6, Asian: 11, H: 16, O: 7	NR 92.5 kg	7.94	6	13

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Bolinder, 2012[17]	Metformin + placebo, 91	60.8	56	C: 100	31.7 90.9 kg	7.16	5.5	20
	Metformin + dapagliflozin, 91	60.6	55.1	C: 100	32.1 92.1 kg	7.19	6	20
Borges, 2011[18]	Metformin, 340	50.7	53	C: 55, AA: 4, Asian: 34, O: 6	NR 90.6 kg	8.6	2.6	154
	Metformin + rosiglitazone, 348	51.5	53	C: 53, AA: 5, Asian: 35, O: 6	NR 87.1 kg	8.6	2.3	131
Cefalu, 2013[20]	Metformin + glimepiride, 484	56.3	55	C: 67, AA: 5, Asian: 19, O: 9	NR 86.5 kg	7.8	6.6	98
	Metformin + canagliflozin, 483	56.4	52	C: 67, AA: 4, Asian: 21, O: 9	NR 86.9 kg	7.8	6.5	88
Chawla, 2013[23]	Metformin + canagliflozin, 485	55.8	50	C: 69, AA: 4, Asian: 19, O: 9	NR 86.6 kg	7.8	6.7	105
	Metformin + pioglitazone, 25	52.2	56	NR	NR 72.6 kg	NR	4.458	0
DeFronzo, 2012[31]	Metformin + sitagliptin, 27	49.48	56	NR	NR 72.1 kg	NR	4.107	2
	Metformin + placebo, 129	55.2	47.3	C: 72.1, AA: 6.2, Asian: 3.9, H: 48.8, O: 17.8	30.6 NR	8.5	6	NR
Derosa, 2011[40]	Metformin + pioglitazone + placebo, 130	54.1	46.9	C: 65.4, AA: 6.2, Asian: 8.5, H: 48.5, O: 20	31.3 NR	8.5	5.7	NR
	Metformin + pioglitazone + placebo, 129	56.1	48.8	C: 74.4, AA: 4.7, Asian: 7.8, H: 51.9, O: 13.2	31.4 NR	8.5	7.6	NR
	Metformin + pioglitazone + placebo, 129	54.5	41.1	C: 65.9, AA: 7, Asian: 9.3, H: 47.3, O: 17.8	30.7 NR	8.5	5.7	NR
Derosa, 2012[41]	Metformin + alogliptin + placebo, 128	53.1	52.3	C: 69.5, AA: 4.7, Asian: 10.9, H: 46.9, O: 14.8	31 NR	8.6	6.2	NR
	Metformin + alogliptin + placebo, 129	53.7	38.8	C: 62, AA: 3.9, Asian: 11.6, H: 48.8, O: 22.5	31.5 NR	8.6	5.6	NR
Derosa, 2013[42]	Metformin + glimepiride, 54	55	48	C: 100	NR 81.4kg	8.8	NR	NR

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + exenatide, 57	56	49	C: 100	NR 80.2kg	8.7	NR	NR
	Metformin + placebo, 87	54.8	51	C: 100	NR 78.6kg	8	5.4	5
	Metformin + sitagliptin, 91	55.9	46	C: 100	NR 78.4kg	8.1	5.8	7
	Metformin + placebo, 87	54.8	51	NR	NR 78.6kg	8	5.4	5
	Metformin + sitagliptin, 91	55.9	46	NR	NR 78.4kg	8.1	5.8	7
Derosa, 2013[43]	Metformin + placebo, 85	56.7	48	C: 100	NR 90.5kg	7.9	7.8	5
	Metformin + exenatide, 86	57.3	50	C: 100	NR 89.0kg	8.1	7.6	5
Diamant, 2010[44]	Metformin + exenatide, 164	NR	NR	NR	NR NR	NR NR	NR NR	NR NR
	Metformin + insulin glargine, 157	NR	NR	NR	NR NR	NR NR	NR NR	NR NR
Erem, 2014[47]	Metformin, 20	52.2	30	NR	NR 87.5 kg	7.62	NR	1
	Pioglitazone, 20	52.5	25	NR	NR 81.9 kg	8.03	NR	1
Esposito, 2011[48]	Metformin, 55	54.9	50.9	NR	NR 83.5kg	8.1	NR	4
	Pioglitazone + pioglitazone, 55	54.2	54.5	NR	NR 84.5kg	8	NR	4
Esteghamati, 2014[49]	Metformin, 43	50.03	47	NR	NR 74.3 kg	8.2	NR	2
	Pioglitazone, 55	51.25	25	NR	NR 77.01	8.1	NR	5
Farcasiu, 2011[51]	Metformin + insulin lispro 75/25, 151	58.4	45.7	C: 98.7, AA: 1.3, O: 1.3	85.1 kg	8.5	11.5	23
	Metformin + insulin lispro 50/50, 151	57	39.1	C: 99.3, AA: 0.7	32.3, 88.6 kg	8.6	10.9	23

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Ferrannini, 2013[53]	Metformin, 56	58	50	C: 69.6, AA: 1.8, Asian: 25	NR 85.8kg	8.15	NR	NR
	Empagliflozin, 106	59	46.2	C: 79.2, AA: 0, Asian: 19.8	NR 82.9kg	7.89	NR	NR
Fidan, 2011[54]	Empagliflozin, 109	59	52.3	C: 77.1, AA:0, Asian: 21.1	NR 84.6kg	8	NR	NR
	Empagliflozin, 109	59	52.3	C: 77.1, AA: 0, Asian: 21.1	NR 84.6kg	8	NR	NR
Fonseca, 2012[56]	Metformin + sitagliptin, 56	60	51.8	C: 100, AA: 0, Asian: 0	NR 88.6	8.03	NR	NR
	Metformin + empagliflozin, 166	60	50	C: 98.2, AA: 1.8, Asian: 0	NR 89.6 kg	7.88	NR	NR
Forst, 2010[57]	Metformin + empagliflozin, 166	60	53	C: 98.8, AA: 1.2, Asian: 0	NR 89.5 kg	7.91	NR	NR
	Metformin, 20	52.6	70	NR	30.1 NR	NR	NR	NR
	Rosiglitazone, 20	54.1	55	NR	30.9 NR	NR	NR	NR
	Metformin, 144	55.5	51	C: 13, AA: 4, H: 61, O: 23	31 NR	8.4	5.9	25
	Metformin + saxagliptin, 138	55.2	41	C: 9, AA: 7, H: 61, O: 23	30.8 NR	8.3	6.5	8
	Metformin + placebo, 71	60.1	62	C: 97, AA: 1, Asian: 1	NR 93.1kg	8.4	6.2	14
	Metformin + glimepiride, 65	59.4	63.1	C: 99, AA: 0, Asian: 2	NR 90.5kg	8.2	6.7	4
Forst, 2012[58]	Metformin + linagliptin, 66	59.6	56.1	C: 100, AA: 0, Asian: 0	NR 90.7kg	8.5	7.3	10
	Metformin, 22	57.9	45	NR	NR 96.9 kg	6.36	4.8	3
Forst, 2014[59]	Metformin + liraglutide, 22	55.1	45	NR	NR 93.2 kg	6.32	3.8	1
	Metformin + glimepiride, 20	63	70	NR	NR 95.1 kg	7.4	8	0

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Gallwitz, 2011[60]	Metformin + linagliptin, 20	65	65	NR	NR 89.6 kg	7.3	7.7	1
	Metformin + exenatide, 182	57	NR	NR	33.4 NR	NR	5	47
	Metformin + insulin aspart 70/30, 181	57	NR	NR	32.9 NR	NR	5	44
Gallwitz, 2012[61]	Metformin + glimepiride + placebo, 775	59.8	61	C: 85, AA: 2, Asian: 12, O: <1	30.3 86.8 kg	7.7	NR	NR
	Metformin + linagliptin + placebo, 777	59.8	60	C: 85, AA: 3, Asian: 12, O: <1	30.2 86.1 kg	7.7	NR	NR
Gallwitz, 2012[62]	Metformin + glimepiride, 514	56	52	C: 91, H: 7, O: 2	32.3 91.1 kg	7.4	5.5	128
	Metformin + exenatide, 515	56	56	C: 92, H: 7, O: <1	32.6 92.8 kg	7.5	5.8	174
Garber, 2011[67]	Glimepiride + placebo, 248	53.4	54	C: 77, AA: 12, Asian: 4, H: 38, O: 7	NR 93.3 kg	8.2	5.6	151
	Liraglutide + placebo, 251	53.7	47	C: 80, AA: 14, Asian: 2, H: 32, O: 5	NR 92.1 kg	8.2	5.2	141
Genovese, 2013[68]	Liraglutide + placebo, 247	52	49	C: 75, AA: 12, Asian: 5, H: 35, O: 8	NR 92.6 kg	8.2	5.3	132
	Metformin + placebo, 103	57.8	60.2	C: 100	NR 89kg	7.02	5.7	6
Genovese, 2013[69]	Metformin + pioglitazone, 110	57	59.1	C: 100	NR 88.8kg	6.92	5.8	13
	Metformin 29	56.4	65.5	NR	NR 87.8kg	6.8	3.9	3
Goke, 2010[70]	Pioglitazone + placebo 29	59.1	48.3	NR	NR 84.1kg	6.9	4.4	5
	Metformin + glipizide 430	57.6	54	C: 84.2, AA: 0, Asian: 15.1, O: 0.7	31.3, 88.6 kg	7.7	5.4	283
	Metformin + saxagliptin 428	57.5	49.5	C: 82.2, AA: 0.2, Asian: 17.1, O: 0.5	31.5 88.7 kg	7.7	5.5	263
Gupta, 2010[75]	Metformin	50.9	NR	NR	25.7 60.5 kg	8.71	NR	NR

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Glipizide	49.5	NR	NR	25.7 57.9 kg	8.59	NR	NR
Gupta, 2013[76]	Rosiglitazone	50.5	NR	NR	24.3 56.4 kg	8.3	NR	NR
	Sitagliptin 84	39.12	NR	NR	25.4 60.2 kg	8.03	NR	7
Haak, 2012[77]	Glimepiride 83	40.07	NR	NR	26.18 61.1 kg	8.02	NR	12
	Metformin 144	52.9	56.9	C: 64.6, AA: 0, Asian: 35.4, O: 0	NR 79.9 kg	8.7	NR	17
Haak, 2012[77]	Metformin 147	55.2	53.1	C: 64.6, AA: 1.4, Asian: 34, O: 0	NR 80 kg	8.5	NR	21
	Linagliptin 142	56.2	56.3	C: 68.3, AA: 0, Asian: 31.7, O: 0	NR 79.1 kg	8.7	NR	21
	Metformin + linagliptin 143	55.6	51	C: 72, AA: 1.4, Asian: 25.9, O: 0.7	NR 80.8 kg	8.7	NR	16
Haak, 2013[78]	Metformin + linagliptin 143	56.4	53.8	C: 65.7, AA: 0.7, Asian: 33.6, O: 0	NR 76.7 kg	8.7	NR	11
	Metformin, 170	55.6	54.1	C: 62.4, AA: 0.9, Asian: 36.7	29.2 NR	7.31	NR	NR
Haring, 2014[83]	Metformin, 170	55.7	55.7	C: 63.9, AA: 0, Asian: 36.1	29.5 NR	7.76	NR	NR
	Metformin + linagliptin, 225	56.8	51.3	C: 71.7, AA: 1.8, Asian: 26.5	29.8 NR	7.34	NR	NR
	Metformin + linagliptin, 225	55.1	55.4	C: 65.2, AA: 0, Asian: 34.8	28.3 NR	7.95	NR	NR
Henry, 2012[84]	Metformin + linagliptin, 171	56.1	61.7	C: 68.3, AA: 0, Asian: 31.7	28.8 NR	8.15	NR	NR
	Metformin + linagliptin, 171	55.6	54.1	C: 60.4, AA: 0.9, Asian: 38.7	28.5 NR	6.93	NR	NR
Henry, 2012[84]	Metformin + placebo, 207	56	56	C: 55, AA: 1, Asian: 44, O: 0	NR 79.7kg	7.9	NR	21
	Metformin + empagliflozin, 217	55.5	58	C: 52, AA: 2, Asian: 46, O: 1	NR 81.6kg	7.94	NR	8

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + empagliflozin, 214	55.6	56	C: 53, AA: 0, Asian: 46, O: 1	NR 82.2kg	7.86	NR	18
	Metformin + placebo, 201	51.8	24	NR	NR 85.6kg	9.2	0.6	30
	Dapagliflozin + placebo, 203	52.3	22	NR	NR 86.2kg	9.1	0.4	33
	Metformin + dapagliflozin, 194	51.7	21	NR	NR 84.1kg	9.2	0.3	17
Hermans, 2012[87]	Metformin + placebo, 208	52.7	46.6	NR	NR 87.2 kg	9.1	0.5	27
	Dapagliflozin + placebo, 219	51.1	47.9	NR	NR 88.5 kg	9.1	0.6	31
	Metformin + dapagliflozin, 211	51	50.2	NR	NR 88.4 kg	9.1	0.6	28
Ji, 2015[93]	Metformin, 344	53.1	49.1	C: 27.9, AA: 0, Asian: 47.4, O: 24.7	29 NR	8	NR	14
	Metformin + Linagliptin, 345	52.9	45.8	C: 22.6, AA: 0.9. Asian: 47.8, O: 28.7	29 NR	8	NR	14
Kadoglou, 2011[95]	Metformin, 139	58.6	54.7	C: 97.1, AA: 0.7, Asian: 1.4, O: 0.7	31.2 NR	NR	6.9	32
	Metformin + saxagliptin, 147	58.7	59.9	C: 98.6, AA: 0.7, Asian: 0.7, O: 0	32.1 NR	NR	6	28
	Metformin, 70	62.7	27	NR	30.04 NR	7.56	2.7	NR
Kadowaki, 2013[96]	Metformin + rosiglitazone, 70	62	26	NR	29.68 NR	7.58	1.8	NR
	Metformin + placebo, 72	57.2	68.1	NR	25 NR	8.4	7.3	NR
	Metformin + sitagliptin, 77	59.6	71.4	NR	25.2 NR	8.2	7.7	NR
Kaku, 2011[99]	Glibenclamide	58.5	65.2	Asian: 100	NR 65.4 kg	9.18	8.5	NR
	Liraglutide	58.2	68.3	Asian: 100	NR 66.2 kg	9.32	8.1	NR

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Kikuchi, 2012[101]	Rosiglitazone 160	55	62.9	Asian: 100	24.5 NR	8.9	5	11
	Pioglitazone 159	56	62.3	Asian: 100	24.9 NR	8.8	4.2	22
Kim, 2014[103]	Metformin 108	56.1	47.2	NR	25.7 66.9 kg	7.8		14
	Metformin + glimepiride 101	55.2	51.5	NR	25.5 66.5 kg	7.9		6
Lavalle-Gonzalez, 2013[106]	Metformin + placebo, 183	55.3	51.4	C: 70.5, AA: 1.6, Asian: 16.4, O: 11.5	NR 86.6kg	8	6.8	28
	Metformin + sitagliptin, 366	55.5	47	C: 72.1, AA: 3.6, Asian: 11.2, O: 13.1	NR 87.7kg	7.9	6.8	47
List, 2009[109]	Metformin + canagliflozin, 368	55.5	47.3	C: 68.5, AA: 4.3, Asian: 13.9, O: 13.3	NR 88.8kg	7.9	6.7	46
	Metformin + canagliflozin, 367	55.3	45	C: 69.8, AA: 3.5, Asian: 16.3, O: 10.4	NR 85.4kg	7.9	7.1	44
Maffioli, 2013[111]	Metformin 56	54	48	NR	NR 88 kg	7.6	NR	5
	Dapagliflozin 58	55	48	NR	NR 89 kg	8	NR	3
Moon, 2014[114]	Dapagliflozin 47	54	53	NR	NR 86 kg	8	NR	7
	Metformin + pioglitazone, 86	62.8	48	NR	NR 83.5 kg	8.4	NR	3
	Metformin + glibenclamide, 84	61.4	50	NR	NR 83.1 kg	8.2	NR	2
	Metformin + glimepiride 36	54.9	47.1	NR	NR 66.0 kg	8.9	95.6	2
Nauck, 2009[119]	Metformin + insulin glargine, 39	51.3	31.6	NR	NR 62.7 kg	8.8	79	0
	Metformin + placebo 104	56	48	C: 76, AA: 7, Asian: 6, H: 24, O: 11	32 NR	8	6	NR
	Metformin + alogliptin 210	54	54.3	C: 76, AA: 6, Asian: 9, H: 32, O: 9	32 NR	7.9	6	NR

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Nauck, 2011[120]	Metformin + alogliptin 213	55	47.4	C: 80, AA: 2, Asian: 8, H: 31, O: 10	32 NR	7.9	6	NR
	Metformin + glipizide 408	59	54.9	C: 80.5, AA: 6, Asian: 8.5, O: 5	31.2 NR	7.7	7	94
Nauck, 2014[121]	Metformin + dapagliflozin 406	58	55.3	C: 81.8, AA: 6.5, Asian: 6.8, O: 5	31.7 NR	7.7	6	84
	Metformin + placebo 177	55	51	C: 51, AA: 5, Asian: 22, H: 22, O: 0	NR 87 kg	8.1	7	NR
Oz Gul, 2010[122]	Metformin + sitagliptin 315	54	48	C: 50, AA: 2, Asian: 26, H: 21, O: 1	NR 86 kg	8.1	7	NR
	Metformin + dulaglutide 302	54	44	C: 54, AA: 4, Asian: 26, H: 17, O: 0	NR 86 kg	8.2	7	NR
	Metformin + dulaglutide 304	54	48	C: 52, AA: 5, Asian: 25, H: 18, O: 0	NR 87 kg	8.1	7	NR
Perez-Monteverde, 2011[124]	Rosiglitazone 20	NR	NR	NR	NR 29.6	7.3	NR	NR
	Pioglitazone 19	NR	NR	NR	29.3 NR	7.6	NR	NR
Petrica, 2009[126]	+ placebo 21	NR	NR	NR	29.6 NR	7.3	NR	NR
	Sitagliptin 248	51.7	59.7	C: 55.2, AA: 4.4, Asian: 12.9, H: 45.2, O: 8.5	NR 82.2kg	9.1	3.5	17
	Pioglitazone 248	51.7	59.7	C: 55.2, AA: 4.4, Asian: 12.9, H: 45.2, O: 8.5	NR 82.2kg	9.1	3.5	17
	Metformin + rosiglitazone 22	63	32	NR	33.55 NR	7.72	10.53	5
Pfutzner, 2011[128]	Metformin + glimepiride 22	63.2	32	NR	33.58 NR	7.58	10.4	5
	Metformin + pioglitazone	59	66	NR	32.6 NR		6.2	32
	Metformin + glimepiride	59	64	NR	32.5 NR		5.9	29

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Pfutzner, 2011[129]	Metformin + placebo 328	51.8	49.7	C: 76.5, AA: 1.2, Asian: 15.9, O: 6.4	30.2 NR	9.4	1.7	109
	Saxagliptin + placebo 335	52.1	50.4	C: 76.1, AA: 1.8, Asian: 16.7, O: 5.4	30.2 NR	9.6	1.7	126
Pratley, 2014[131]	Metformin + saxagliptin 320	52	51.6	C: 76.9, AA: 2.2, Asian: 15.9, O: 5	29.9 NR	9.4	2	91
	Metformin + saxagliptin 323	52.1	45.2	C: 75.2, AA: 2.2, Asian: 16.7, O: 5.9	30.4 NR	9.5	1.4	92
Qiu, 2014[132]	Metformin 114	54.6	41.2	C: 74.6, AA: 5.3, Asian: 16.7, O: 3.5	30.2 NR	8.5	3.8	NR
	Metformin 111	52.6	45.9	C: 71.2, AA: 5.4, Asian: 18, O: 5.4	30.5 NR	8.39	4.1	NR
Reasner, 2011[135]	Metformin + alogliptin 111	53.7	43.2	C: 68.5, AA: 5.4, Asian: 18, O: 8.1	30.9 NR	8.5	4.1	NR
	Metformin + alogliptin 114	54.6	54.4	C: 68.4, AA: 4.4, Asian: 22.8, O: 4.4	31 NR	8.43	4.2	NR
	+ alogliptin 112	52.6	42.9	C: 75, AA: 2.7, Asian: 15.2, O: 7.1	30.8 NR	8.3	3.6	NR
	Metformin + placebo 93	57	49.5	C: 78.5, AA: 4.3, Asian: 9.7, O: 7.5	NR 90.5kg	7.7	7	7
Ridderstrale, 2014[136]	Metformin + canagliflozin 93	58.6	43	C: 80.6, AA: 5.4, Asian: 3.2, O: 10.8	NR 91.2kg	7.6	6.7	8
	Metformin + canagliflozin 93	56.7	47.3	C: 89.2, AA: 1.1, Asian: 6.5, O: 3.2	NR 90.2kg	7.6	7.3	13
	Metformin	50	57	C: 79, AA: 14, Asian: 4, H: 30, O: 3	33.7 97.2 kg	9.8	3.2	215
	Metformin + sitagliptin	49.4	56	C: 81, AA: 13, Asian: 3, H: 36, O: 3	32.9 94.7 kg	9.9	3.5	216
	Metformin + glimepiride 780	55.7	54	C: 67, AA: 1, Asian: 32, H: 20, O: 0	NR 83.0kg	7.92	NR	132
Roden, 2013[139]	Metformin + empagliflozin, 769	56.2	56	C: 65, AA: 2, Asian: 33, H: 20, O: <1	NR 82.5kg	7.92	NR	121
	Sitagliptin 223	55.1	63	C: 34, AA: 1, Asian: 64, O: <1	NR 79.3kg	7.85	NR	17

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Sitagliptin 223	55.1	63	C: 34, AA: 1, Asian: 64, O: <1	NR 79.3kg	7.85	NR	17
Rosenstock, 2010[141]	Empagliflozin 224	56.2	63	C: 34, AA: 1, Asian: 64, O: 0	NR 78.4kg	7.87	NR	18
	Empagliflozin 224	53.8	65	C: 33, AA: 3, Asian: 64, O: 0	NR 77.8kg	7.86	NR	20
Rosenstock, 2012[142]	Pioglitazone + placebo 163	NR	NR	NR	NR NR	8.76	NR	37
	Alogliptin + placebo 164	NR	NR	NR	NR NR	8.8	NR	38
Rosenstock, 2013[143]	Metformin + placebo 65	53.3	48	NR	NR 85.9 kg	7.75	6.4	10
	Metformin + sitagliptin 65	51.7	58	NR	NR 87.2 kg	7.64	5.6	5
	Metformin + canagliflozin 64	51.7	56	NR	NR 87.7 kg	7.83	6.1	5
	Metformin + canagliflozin 65	52.9	51	NR	NR 87.7 kg	7.61	6.4	9
Rosenstock, 2013[144]	Metformin + canagliflozin 64	52.3	56	NR	NR 87.3 kg	7.69	5.9	8
	Alogliptin 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02 NR	7.45	5.94	NR
Ross, 2012[146]	Glipizide 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02 NR	7.45	5.94	NR
	Metformin + placebo 71	60	47	C: 90, AA: 1, H: 9, O: 0	NR 87.7kg	8	NR	5
	Metformin + sitagliptin 71	58	54	C: 87, AA: 0, H: 13, O: 0	NR 88.0kg	8.1	NR	1
	Metformin + empagliflozin, 71	59	47	C: 78, AA: 3, H: 20, O: 0	NR 87.9kg	7.9	NR	5
	Metformin + empagliflozin, 70	59	53	C: 83, AA: 1, H: 16, O: 0	NR 90.5kg	8.1	NR	0
Russell-Jones,	Metformin + placebo 44	59.9	47.7	C: 72.7, Asian: 27.3, O: 0	NR 77.7kg	7.92	NR	1

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
2012[147]	Metformin + linagliptin + placebo, 224	58.4	54	C: 62.1, Asian: 36.6, O: 1.3	NR 80.6kg	7.98		10
Schernthaner, 2015[148]	Metformin + glimepiride + placebo, 360	72.5	60.3	C: 97.8, O: 2.2	29.9 NR	7.58	NR	71
	Metformin + saxagliptin + placebo, 360	72.7	63.3	C: 98.6, O: 1.4	29.3 NR	7.62	NR	75
Schondorf, 2011[150]	Metformin + placebo 246	54	62.6	C: 65, AA: 4.5, Asian: 20.7, H: 8.5, O: 1.2	NR 85.9 kg	8.6	2.6	NR
	Pioglitazone + placebo 163	55	59.5	C: 67.5, AA: 2.5, Asian: 20.9, H: 9.2, O: 0	86.1 kg NR	8.5	2.7	NR
	Sitagliptin + placebo 163	52	57.7	C: 69.3, AA: 1.8, Asian: 20.2, H: 8, O: 0.6	NR 88.7 kg	8.5	2.7	NR
	Exenatide + placebo 248	54	56	C: 68.1, AA: 2.8, Asian: 22.2, H: 6.5, O: 0.4	NR 87.5 kg	8.5	2.7	NR
Seino, 2012[156]	Metformin + pioglitazone + placebo, 25	59.4	76	NR	32 NR	7.4	6.7	NR
	Metformin + glimepiride 21	57.5	67	NR	32 NR	6.7	5.9	NR
Shihara, 2011[157]	Metformin + placebo 100	52.1	72	NR	NR 69.9 kg	8	6.04	0
	Metformin + alogliptin 92	53.4	65.2	NR	NR 69.5 kg	7.89	6.34	1
	Metformin + alogliptin 96	52.3	68.8	NR	NR 69.7kg	8.02	6.62	3
	Pioglitazone 96	56.8	68	Asian: 100	NR 65.5 kg	7.8	4.1	5
Srivastava, 2012[158]	SU 95	57.7	65	Asian: 100	NR 65.6 kg	7.8	6	9
	Metformin + glimepiride 25	NR	NR	Asian: 100	26.5 NR	NR	NR	0
Taskinen, 2011[164]	Metformin + sitagliptin 25	NR	NR	Asian: 100	25.3 NR	NR	NR	0
	Metformin + placebo 177	56.6	57	C: 79, Asian: 18, O: 3	NR 83.3 kg	8.02	NR	14

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + linagliptin 523	56.5	53	C: 75, Asian: 22, O: 3	NR 82.2 kg	8.09	NR	39
Taslimi, 2013[165]	Metformin 30	51	50	NR	NR 76.8kg	8.4	24	NR
	Pioglitazone 30	56	43	NR	NR 73.8kg	8.2	36	NR
Umpierrez, 2014[171]	Metformin + placebo 268	55	45	C: 75, AA: 5, Asian: 8, H: 35, O: 13	33, 92 kg	7.6	3	55
	Dulaglutide + placebo 270	56	44	C: 73, AA: 8, Asian: 7, H: 32, O: 11	33, 92 kg	7.6	3	52
Wang, 2015[173]	Metformin + placebo, 205	55.1	49.8	Asian: 100	25.5 NR	7.99	NR	14
	Metformin + linagliptin, 101	56.5	50	Asian: 100	25.8 NR	8	NR	12
White, 2014[175]	Dulaglutide + placebo 269	56	42	C: 75, AA: 6, Asian: 8, H: 33, O: 12	34, 93 kg	7.6	3	49
	Metformin + placebo 86	56.6	52.3	C: 93, AA: 3.5, Asian: 2.3, H: 40.7, O: 1.2	32.5 NR	7.97	6.2	NR
Williams-Herman, 2010[177]	Metformin + saxagliptin 74	53.9	54.1	C: 86.5, AA: 10.8, Asian: 2.7, H: 39.2, O: 0	33.7 NR	7.92	5.8	NR
	Metformin + placebo, 42	54.1	50	NR	31.9 NR	8.1	4	20
Yang, 2011[180] Yang, 2011[180]	Metformin + placebo, 65	55.9	46	NR	32.2 NR	8.6	4	27
	Metformin + placebo, 88	54.3	44	NR	31.9 NR	8.5	3.9	26
	Sitagliptin + placebo, 52	54.1	58	NR	30.3 NR	8.5	3.7	38
Yang, 2012[182]	Metformin + sitagliptin, 100	54.5	50	NR	31.6 NR	8.7	3.7	36
	Metformin + sitagliptin, 107	53.9	37	NR	31.4 NR	8.6	4.4	21
	Metformin + placebo 287	54.4	48.4	Asian: 100	NR 69.0 kg	7.9	5.1	40

Author, year	Group, N	Mean age (age range)	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Yoon, 2011[183]	Metformin + saxagliptin 283	53.8	48.1	Asian: 100	NR 68.9 kg	7.9	5.1	29
	Metformin + glimepiride + placebo, 231	53.6	58.4	Asian: 100	NR 68.2 kg	8.5	7.8	NR
	Metformin + liraglutide + placebo, 231	53.5	54.1	Asian: 100	NR 68.6 kg	8.5	7.4	NR
	Metformin + liraglutide + placebo, 233	53.5	54.9	Asian: 100	NR 67.4 kg	8.6	7.5	NR
	Metformin + liraglutide + placebo, 234	52.7	53.8	Asian: 100	NR 68.2 kg	8.6	7.2	NR
Yuan, 2012[184]	Metformin + placebo, 198	55.1	55	Asian: 100	NR 68.9 kg	NR	7.3	16
	Metformin + sitagliptin, 197	54.1	47	Asian: 100	NR 67.9 kg	NR	6.4	23
	Metformin 114	51.8	57.89	Asian: 100	NR 68.9 kg	7.9	NR	43
	Rosiglitazone 117	50.1	52.14	Asian: 100	NR 69.1 kg	7.8	NR	43
	Glimepiride 118	50.8	55.93	Asian: 100	NR 67.9 kg	7.8	NR	36
	Metformin 26	56.8	46	NR	NR 83.7kg	8.11	NR	0
Zhang, 2012[187]	Exenatide 33	58.5	52	NR	NR 82.2kg	8.27	NR	1
	Metformin + glimepiride 23	52	57	NR	24.8 NR	9	4.1	5
	Metformin + exenatide 19	50.2	53	NR	24.9 NR	8.7	4.2	6

Abbreviations: AA = African American; BHI = biphasic human insulin; BMI = body mass index; C = Caucasian; H = Hispanic; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptidase-1; HbA1c = glycated hemoglobin; kg = kilogram; NPH = neutral protamine Hagedorn; NR = Not Reported; O = Other; SU = sulfonylurea; sd = standard deviation;

Some data may not have been extracted because the question was not asked.

Table D3. Results of studies evaluating effects of diabetes medications on intermediate outcomes

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Aaboe, 2010[1]	Grp1: Metformin + sitagliptin Fixed (100mg daily) Grp2: Metformin + placebo ITT: NR Followup (wks): 12	Grp1: F: 7.25 (6.6-8.2) F-B: -1 (-2.2-0.5) p 0.005 Grp2: F: 7.25 (6.6-8.2) F-B: -0.1 (-3.9-0.9) p NS Between-group difference: p 0.1	Grp1: F: 101.7 (83-125) Grp2: F: 100.5 (83-125)		
Ahren, 2014[2]	Grp1: Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Grp2: Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) ITT: Yes Followup (wks): 104	Grp1: B: 8.2 (0.9) F: 8.4 (0.12) F-B: 0.27 Grp2: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.36 Between-group difference: Grp1: 0.9 (0.7-1.2) p <0.0001 Grp2: 0.3 (0.1-0.5) p 0.0033	Grp1: B: 91.7 (1.2) F: 90.7 (1.6) F-B: -1 Grp2: B: 89.6 (0.6) F: 88.4 (1) F-B: -1.21	Grp1: B: 128.1 (13.2) F-B: 2.2 (14) Grp2: B: 127.4 (13.6) F-B: 0.2 (14.7)	Grp1: B: 72 (11.2) F-B: 2.3 (9.5) Grp2: B: 73.1 (10.2) F-B: 1.3 (10.3)
Ahren, 2014[2]	Grp1: Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Grp2: Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT: Yes Followup (wks): 104	Grp1: B: 8.2 (0.9) F: 8.4 (0.12) F-B: 0.27 Grp2: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.28 Between-group difference: Grp1: 0.9 (0.7-1.2) p <0.0001 Grp2: 0.4 (0.2-0.5) p 0.0001	Grp1: B: 91.7 (1.2) F: 90.7 (1.6) F-B: -1 Grp2: B: 91.9 (1.6) F: 93 (0.9) F-B: 1.17 Between-group difference: p <0.0001	Grp1: B: 128.1 (13.2) F-B: 2.2 (14) Grp2: B: 127.9 (14.3) F-B: 1.5 (14.1)	Grp1: B: 72 (11.2) F-B: 2.3 (9.5) Grp2: B: 73.1 (10.2) F-B: 0.8 (10.7)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Ahren, 2014[2]	Grp1: Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Grp2: Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT: Yes Followup (wks): 104	Grp1: B: 8.2 (0.9) F: 8.4 (0.12) F-B: 0.27 Grp2: B: 8.1 (0.8) F: 7.5 (0.06) F-B: -0.63 Between-group difference: Grp1: 0.9 (0.7-1.2) p <0.0001	Grp1: B: 91.7 (1.2) F: 90.7 (1.6) F-B: -1 Grp2: B: 90.4 (1.6) F: 89.5 (0.9) F-B: -0.86	Grp1: B: 128.1 (13.2) F-B: 2.2 (14) Grp2: B: 128.4 (13.9) F-B: -1 (14.2)	Grp1: B: 72 (11.2) F-B: 2.3 (9.5) Grp2: B: 72 (9.5) F-B: -0.5 (9.6)
Ahren, 2014[2]	Grp1: Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2: Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT: Yes Followup (wks): 104	Grp1: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.36 Grp2: B: 8.1 (0.8) F: 7.5 (0.06) F-B: -0.63 Between-group difference: Grp1: 0.3 (0.1-0.5) p 0.0033	Grp1: B: 91.9 (1.6) F: 93 (0.9) F-B: 1.17 Grp2: B: 89.6 (0.6) F: 88.4 (1) F-B: -1.21 Between-group difference: p <0.0001	Grp1: B: 127.9 (14.3) F-B: 1.5 (14.1) Grp2: B: 127.4 (13.6) F-B: 0.2 (14.7)	Grp1: B: 72 (9.5) F-B: -0.5 (9.6) Grp2: B: 73.1 (10.2) F-B: 0.8 (10.7)
Ahren, 2014[2]	Grp1: Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2: Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd)	Grp1: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.36 Grp2: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.28 Between-group difference: Grp1: 0.3 (0.1-0.5) p 0.0033	Grp1: B: 91.9 (1.6) F: 93 (0.9) F-B: 1.17 Grp2: B: 90.4 (1.6) F: 89.5 (0.9) F-B: -0.86 Between-group difference: p <0.0001	Grp1: B: 127.9 (14.3) F-B: 1.5 (14.1) Grp2: B: 128.4 (13.9) F-B: -1 (14.2)	Grp1: B: 72 (9.5) F-B: -0.5 (9.6) Grp2: B: 73.1 (10.2) F-B: 1.3 (10.3)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	ITT: Yes Followup (wks): 104	Grp2: 0.4 (0.2-0.5) p 0.0001			
Ahren, 2014[2]	Grp1: Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) Grp2: Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qw up-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT: Yes Followup (wks): 104	Grp1: B: 8.1 (0.8) F: 7.8 (0.07) F-B: -0.28 Grp2: B: 8.1 (0.8) F: 7.5 (0.06) F-B: -0.63 Between-group difference: Grp1: 0.4 (0.2-0.5) p 0.0001	Grp1: B: 90.4 (1.6) F: 89.5 (0.9) F-B: -0.86 Grp2: B: 89.6 (0.6) F: 88.4 (1) F-B: -1.21	Grp1: B: 127.4 (13.6) F-B: 0.2 (14.7) Grp2: B: 128.4 (13.9) F-B: -1 (14.2) p	Grp1: B: 73.1 (10.2) F-B: 0.8 (10.7) Grp2: B: 73.1 (10.2) F-B: 1.3 (10.3)
Alba, 2013[3]	Grp1: Pioglitazone Fixed (30mg) Grp2: Sitagliptin Fixed (100mg) ITT: NR Followup (wks): 12	Grp1: B: 7.9 (0.9) F-B: -0.56 (-0.85-0.27) p <0.001 Grp2: B: 7.7 (0.8) F-B: -0.79 (-1.08-0.49) p <0.001			
Amador-Licona, 2000[186]	Grp1: Metformin Varied Start: 850 mg, Max: NR Grp2: Glibenclamide Varied Start: 5 mg, Max: NR	Grp1 B: 8.5 (1.5) F: 7.6 (0.8) F-B: -0.9 p: 0.003 Grp2 B: 8.4 (1.4) F: 7.6 (0.8) F-B: -0.8 p: 0.009 Grp1-Grp2: -0.1	Grp1 B: 70.7 (14.8) F: 69.6 (14.3) F-B: -0.9 p: 0.07 Grp2 B: 73.2 (11.8) F: 74.1 (12.6) F-B: 0.9 p: 0.1 Grp1-Grp2: -1.7		
Apovian, 2010[4]	Grp1: Metformin Fixed Grp2: Metformin + exenatide Fixed Titrated (Max: 10ug twice daily) ITT: No Followup (wks): 24	Grp1: F-B: -0.4 (0.1) p </=0.0009 Grp2: F-B: -0.9 (0.1) p </=0.0009 Between-group difference:	Grp1: F-B: -4.3 (0.7) p <0.05 Grp2: F-B: -7.3 (0.7) p <0.05 Between-group difference: p <0.01		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		p 0.0002			
Arechavaleta, 2011[5]	Grp1: Metformin + glimepiride + placebo Not specified Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2: Metformin + sitagliptin + placebo Not specified Fixed (100mg daily) ITT: No Followup (wks): 30	Grp1: B: 7.51 (0.76) F: 7.02 (0.92) F-B: -0.52 (-0.6-0.45) Grp2: B: 7.5 (0.7) F: 7.09 (0.86) F-B: -0.46 (-0.54-0.38) Between-group difference: Grp2: 0.07 (-0.02-0.16)	Grp1: B: 82 (16.7) F-B: 1.2 (0.9-1.5) Grp2: B: 80.6 (15.2) F-B: -0.8 (-1.1--0.5) Between-group difference: Grp2: -2 p <0.001		
Arjona Ferreira, 2013[6]	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: No Followup (wks): 54	Grp1: B: 7.8 (0.7) F-B: -0.6 (-0.8-0.5) Grp2: B: 7.8 (0.7) F-B: -0.8 (-0.9-0.6) Between-group difference: Grp2: -0.11 (-0.29-0.06)	Grp1: B: 70.2 (15.9) F-B: 1.2 (0.2) Grp2: B: 68 (14.8) F-B: -0.6 (0.2) Between-group difference: Grp2: -1.8 p <0.001		
Aschner, 2010[7]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg, Mean: 1903 D: 5 Wks Grp2: Sitagliptin Fixed	Grp1 F-B: -0.55 (CI: -0.61, -0.5) Grp2 F-B: -0.38 (CI: -0.43, -0.32) Grp1-Grp2: -0.18 (CI: -	Grp1 F-B: -1.9 (CI: -2.2, -1.7) Grp2 F-B: -0.6 (CI: -0.9, -0.4) Grp1-Grp2: -1.3 p:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Mean: 100 mg	0.25, -0.1)	<0.001		
Aschner, 2012[8]	Grp1: Metformin + sitagliptin Not specified Fixed (100 mg) Grp2: Metformin + insulin glargine Not specified Titrated (0.5 U/kg at 24 wks) ITT: No Followup (wks): 24	Grp1: F-B: -1.13 (0.06) Grp2: F-B: -1.72 (0.06) Between-group difference: Grp2: -0.59 (-0.77-0.42) p <0.0001	Grp1: F-B: -1.08 (0.2) Grp2: F-B: 0.44 (0.22) Between-group difference: Grp2: 1.51 (0.93-2.09) p <0.0001		
Bailey, 2005[9]	Grp1: Metformin Varied Start: 2500 mg, Max: 3000 mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 2000 mg; Start: 4 mg, Max: 8 mg	Grp1 B: 7.5 (1.0) F: 7.4 (1.1) F-B: -0.13 Grp2 B: 7.4 (1.0) F: 7.1 (1.1) F-B: -0.33 Grp1-Grp2: 0.22 p: 0.001	Grp1 B: 89.5 (14.4) F: 88.6 F-B: -0.9 (SE: 0.2) Grp2 B: 90.9 (15.6) F: 92.2 F-B: 1.3 (SE: 0.22) Grp1-Grp2: -2.2		
Bailey, 2013[10]	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT: No Followup (wks): 102	Grp1: B: 8.12 (0.96) F-B: 0.02 (-0.2-0.23) Grp2: B: 7.92 (0.82) F-B: -0.78 (-0.97-0.68) Between-group difference: Grp2: -0.8 (-1.08-0.52) p <0.0001	Grp1: B: 87.74 (19.24) F-B: 1.36 (0.53-2.2) Grp2: B: 84.73 (16.26) F-B: -1.7 (-2.48--0.91) Between-group difference: Grp2: -3.06 (-4.21--1.92) p <0.0001	Grp1: B: 128 (15) F-B: 1.5 (13.7) Grp2: B: 127 (14) F-B: 0.7 (16.1) Between-group difference: p 0.1111	
Bailey, 2013[10]	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin Fixed (Mean: 1854 mg Median: 2000 mg) Fixed (5.0 mg) ITT: No Followup (wks): 102	Grp1: B: 8.12 (0.96) F-B: 0.02 (-0.2-0.23) Grp2: B: 8.17 (0.96) F-B: -0.58 (-0.77-0.39) Between-group difference:	Grp1: B: 87.74 (19.24) F-B: 1.36 (0.53-2.2) Grp2: B: 86.28 (17.53) F-B: -1.74 (-2.51--0.96) Between-group difference: Grp2: -3.1 (-4.24--1.96)	Grp1: B: 128 (15) F-B: 1.5 (13.7) Grp2: B: 126 (16) F-B: -0.3 (15) Between-group difference: p 0.0067	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Grp2: -0.6 (-0.89-0.31) p <0.0001	p <0.0001		
Bailey, 2013[10]	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mg Median: 1500 mg) Fixed (2.5 mg) ITT: No Followup (wks): 102	Grp1: B: 8.12 (0.96) F-B: 0.02 (-0.2-0.23) Grp2: B: 7.99 (0.9) F-B: -0.48 (-0.68-0.29) p Between-group difference: Grp2: -0.5 (-0.79-0.21) p 0.0008	Grp1: B: 87.74 (19.24) F-B: 1.36 (0.53-2.2) Grp2: B: 84.9 (17.77) F-B: -1.1 (-1.91--0.29) Between-group difference: Grp2: -2.46 (-3.63--1.3) p <0.0001	Grp1: B: 128 (15) F-B: 1.5 (13.7) Grp2: B: 127 (14) F-B: -1.1 (13.2) Between-group difference: p 0.0136	
Bakris, 2003[11]	Grp1: Rosiglitazone Fixed Start: 4 mg bid Grp2: Glyburide Varied Start: NR, Max: 20 mg	Grp1 B: 9.1 (1.68) F: 8.2 F-B: -0.9 (1.38) Grp2 B: 9.5 (1.59) F: 8.6 F-B: -0.9 (1.39) Grp1-Grp2: 0 p: NS			
Bakris, 2006[12]	Grp1: Metformin + rosiglitazone Varied; Varied, glucose: <=6.6 mmol/L Unclear; Start: 4 mg D: 3 wks Grp2: Metformin + glyburide Varied; Glucose: <=6.6 mmol/L Unclear; Start: 5 mg D: 3 wks; NR	Grp1 F-B: 0.72 (SE: 0.1) Grp2 F-B: 0.92 (SE: 0.08) Grp1-Grp2: -0.2 (SE: 0.12)	Grp1 F-B: 1.94 (4.63) Grp2 F-B: 1.5 (3.53) Grp1-Grp2: 0.44		
Barnett, 2012[13]	Grp1: Glimepiride Titrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg qd and uptitrated in 1mg increments every 4 wks to 4mg qd max if 88asting blood glucose was >110mg/dl (6.1mmol/l)) Grp2: Linagliptin Fixed (5mg qdstarted this at	Grp1: B: 8.1 (0.9) F-B: -0.72 (0.15) Grp2: B: 8.1 (1) F-B: -0.44 (0.1)	Grp1: B: 80.9 (19.1) F-B: 1.3 (0.57) Grp2: B: 77 (18.8) F-B: -0.2 (0.42)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	randomization and on for all 52 wks) ITT: No Followup (wks): 52				
Bergenstal, 2010[14]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.1) F: 7.4 (0.1) F-B: -1.2 (-1.4-1) Grp2: B: 8.5 (1.2) F: 7.7 (0.1) p F-B: -0.9 (-1.1-0.7) Between-group difference: Grp1: 0.3 (0.1-0.6) p 0.0165 Grp2: 0.6 (0.4-0.9) p <0.0001	Grp1: B: 88 (20) F-B: 2.8 (2.2-3.4) Grp2: B: 87 (20) F-B: -0.8 (-1.4--0.1) Between-group difference: Grp1: 5.1 (4.3-5.9) p <0.0001 Grp2: 1.5 (0.7-2.4) p 0.0002	Grp1: B: 127 (14) F-B: -1.6 (1) Grp2: B: 126 (14) F-B: -3.6 (1) Between-group difference: p NS	
Bergenstal, 2010[14]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.1) F: 7.4 (0.1) p F-B: -1.2 (-1.4-1) Grp2: B: 8.6 (1.2) F: 7.2 (0.1) F-B: -1.5 (-1.7-1.4) Between-group difference: Grp1: 0.3 (0.1-0.6) p 0.0165	Grp1: B: 88 (20) F-B: 2.8 (2.2-3.4) Grp2: B: 89 (20) F-B: -2.3 (-2.9--1.7) Between-group difference: Grp1: 5.1 (4.3-5.9) p <0.0001	Grp1: B: 127 (14) F-B: -1.6 (1) Grp2: B: 126 (14) F-B: 0.19 (0.6) Between-group difference: p NS Grp2: 4 (1-6) p 0.0055	
Bergenstal, 2010[14]	Grp1: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.2) F: 7.7 (0.1) F-B: -0.9 (-1.1-0.7) Grp2: B: 8.6 (1.2) F: 7.2 (0.1) F-B: -1.5 (-1.7-1.4) Between-group difference:	Grp1: B: 87 (20) F-B: -0.8 (-1.4--0.1) Grp2: B: 89 (20) F-B: -2.3 (-2.9--1.7) Between-group difference: Grp1: 1.5 (0.7-2.4) p 0.0002	Grp1: B: 126 (14) F-B: 0.19 (0.6) Grp2: B: 126 (14) F-B: -3.6 (1) Between-group difference: Grp1: 4 (1-6) p 0.0055	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Grp1: 0.6 (0.4-0.9) p <0.0001			
Bergenstal, 2012[15]	Grp1: Metformin + placebo Fixed (Stable dose of >/=1,500mg/day) Grp2: Metformin + sitagliptin + placebo Fixed (Stable dose of >/=1,500mg/day) Fixed (100mg QD) ITT: NR Followup (wks): 24	Grp1: B: 8.03 (0.83) F: 7.9 (0.2) F-B: -0.1 (0.08) Grp2: B: 7.94 (0.85) F: 7.2 (0.1) F-B: -0.89 (0.06)	Grp1: B: 91.1 (19) F-B: -0.5 (0.4) Grp2: B: 92.5 (19.7) F-B: -0.9 (0.3)		
Blonde, 2002[16]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Fixed Start: 10 mg bid	Grp1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 Grp2 B: 9.64 (1.44) F: 9.5 F-B: -0.11 Grp1-Grp2: 0.5	Grp1 B: 89.5 (16.9) F: 87.5 F-B: -2 Grp2 B: 88 (15.9) F: 88.5 F-B: 0.5 Grp1-Grp2: -2.5		
Blonde, 2002[16]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	Grp1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 Grp2 B: 9.42 (1.24) F: 7.9 F-B: -1.38 Grp1-Grp2: 1.77 p: <0.001			
Blonde, 2002[16]	Grp1: Metformin Varied Start: 500 mg , Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Grp1 B: 9.51 (1.34) F: 9.7 F-B: 0.39 Grp2 B: 9.41 (1.47) F: 7.9 F-B: -1.64 Grp1-Grp2: 2.03 p: <0.001			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Bolinder, 2012[17]	Grp1: Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment) Grp2: Metformin + dapagliflozin Fixed (10 mg) ITT: NR Followup (wks): 102	Grp1: B: 7.16 (0.53) F-B: 0.12 (-0.02-0.27) Grp2: B: 7.19 (0.44) F-B: -0.3 (-0.43-0.16) Between-group difference: Grp2: -0.42 (-0.62-0.22) p	Grp1: B: 90.9 (13.7) F-B: -2.12 (-2.97--1.27) Grp2: B: 92.1 (14.1) F-B: -4.54 (-5.43--3.66) Between-group difference: Grp2: -2.42 (-3.64--1.21) p	Grp1: B: 133.3 (13.7) F-B: 1.1 (-1.4-3.7) Grp2: B: 136.1 (13.8) F-B: -1.3 (-4.3-1.7)	Grp1: B: 71.9 (7.8) F-B: 1.5 (-0.6-3.6) p Grp2: B: 70.9 (10) F-B: 1.6 (-0.4-3.6) p
Borges, 2011[18]	Grp1: Metformin Titrated (Max: 2000 mg/dStart 500mg/d) Grp2: Metformin + rosiglitazone Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT: No Followup (wks): 80	Grp1: B: 8.6 (0.9) F-B: -1.7 (0.1) Grp2: B: 8.6 (0.9) F-B: -1.9 (0.1)	Grp1: F-B: -3.37 Grp2: F-B: 1.42		
Campbell, 1994[19]	Grp1: Metformin Varied Start: 500 mg bid, Max: 3000 mg Grp2: Glipizide Varied Start: 5 mg, Max: 30 mg	Grp1 B: 11.46 (1.92) F: 8.64 (1.21) F-B: -2.57 Grp2 B: 11.75 (2.11) F: 9.72 (1.91) F-B: -1.93 Grp1-Grp2: -0.64 p: <0.05	Grp1 B: 78.2 (15.7) F: 76.23 F-B: -1.97 Grp2 B: 82.2 (16.8) F: 84.8 F-B: 2.67 Grp1-Grp2: -4.57 p: <0.001		
Cefalu, 2013[20]	Grp1: Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the	Grp1: B: 7.8 (0.8) F-B: -0.81 (0.04) Grp2: B: 7.8 (0.8) F-B: -0.93 (0.04) Between-group difference: Grp2: -0.12 (-0.22-0.02)	Grp1: B: 86.6 (19.8) F-B: 0.7 (0.2) Grp2: B: 86.6 (19.3) F-B: -4 (0.2) Between-group difference: Grp2: -4.7 (-5.2--4.3)	Grp1: B: 129.5 (13.5) F-B: 0.2 (0.6) Grp2: B: 130 (12.4) F-B: -3.3 (0.6) Between-group difference: Grp2: -3.5 (-4.9-2.1)	Grp1: B: 73.5 F-B: 0.5 (8.3) Grp2: B: 74.2 F-B: -1.1 (8.5)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	investigational site)) Grp2: Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (300mg) ITT: No Followup (wks): 52				
Cefalu, 2013[20]	Grp1: Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2: Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (100mg) ITT: No Followup (wks): 52	Grp1: B: 7.8 (0.8) F-B: -0.81 (0.04) Grp2: B: 7.8 (0.8) F-B: -0.82 (0.04) Between-group difference: Grp2: -0.01 (-0.11-0.09)	Grp1: B: 86.6 (19.8) F-B: 0.7 (0.2) Grp2: B: 86.8 (20) F-B: -3.7 (0.2) Between-group difference: Grp2: -4.4 (-4.8--3.9)	Grp1: B: 129.5 (13.5) F-B: 0.2 (0.6) Grp2: B: 130 (13.8) F-B: -4.6 (0.6) Between-group difference: Grp2: -4.8 (-6.2-3.4) p	Grp1: B: 73.5 F-B: 0.5 (8.3) Grp2: B: 74.6 F-B: -1.2 (8.7)
Charbonnel, 2006[21]	Grp1: Metformin Varied, glucose: , HbA1c: 7% - 10% Start: >=1500 mg D: 19 wks Grp2: Metformin + sitagliptin Varied; Fixed Start: >=1500 mg; Mean: 100 mg D: 19 wks	Grp1 B: 8.03 (0.82) F: 7.95 (1.1) F-B: -0.02 (CI: -0.15, 0.1) Grp2 B: 7.96 (0.81) F: 7.26 (0.97) F-B: -0.67 (CI:	Grp1 F-B: 0.6-0.7 p: <0.05 Grp2 F-B: 0.6-0.7 p: <0.05 Grp1-Grp2: p=0.835		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		-0.77, -0.57) Grp1-Grp2: 0.65 (SE 0.08)			
Charpentier, 2001[22]	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Glimepiride Varied Start: 1 mg, Max: 6 mg	Grp1 B: 6.79 (1.17) F: 6.86 (1.45) F-B: 0.07 (SE: 0.14) Grp2 B: 6.52 (1.13) F: 6.79 (1.43) F-B: 0.27 (SE: 0.09) Grp1-Grp2: -0.12 p: 0.369	Grp1 B: 82.2 F: 81.46 F-B: -0.74 (2.58) Grp2 B: 81 F: 81.78 F-B: 0.78 (2.98) Grp1-Grp2: -1.52		
Charpentier, 2001[22]	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Metformin + glimepiride Fixed; Varied Start: 850 mg tid; Start: 1 mg, Max: 6 mg	Grp1 B: 6.79 (1.17) F: 6.86 (1.45) F-B: 0.07 (SE: 0.14) Grp2 B: 6.42 (1.08) F: 5.68 (0.99) F-B: -0.74 (SE: 0.8) Grp1-Grp2: 0.92 p: <0.001	Grp1 B: 82.2 F: 81.46 F-B: -0.74 (2.58) Grp2 B: 81.2 F: 81.8 F-B: 0.6 (2.86) Grp1-Grp2: -1.34		
Chawla, 2013[23]	Grp1: Metformin + pioglitazone Fixed (usual doses as that prior to the studyMean: 1830mg) Fixed (30mg) Grp2: Metformin + sitagliptin Fixed (usual doses as that prior to the studyMean: 1865.38) Fixed (100mg) ITT: No Followup (wks): 16	Grp1: B: 8.228 (0.822) F: 7.48 (0.662) F-B: -0.748 (0.35) p <0.0001 Grp2: B: 8.076 (0.722) F: 7.42 (0.661) F-B: -0.656 (0.21) p <0.0001 Between-group difference: p 0.268	Grp1: B: 72.68 (10.76) F-B: 0.9 Grp2: B: 72.1 (13.8) F-B: -0.58		
Chien, 2007[24]	Grp1: Metformin Varied, glucose: <140 mg/dL	Grp1 B: 8.88 (1.08)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 1000 mg, Max: 2000 mg, Final mean dose: 1910 mg D: 4 wks Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 10 mg, Max: 20 mg, Final mean dose: 19 mg D: 4 wks	F: 8.98 F-B: 0.09 (SE: 0.37) p: NS Grp2 B: 8.69 (0.94) F: 9.21 F-B: 0.52 (SE: 0.24) p: 0.018 Grp1-Grp2: -0.43 (SE: 0.44)			
Chien, 2007[24]	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1723 mg; Start: 10 mg, Max: 20 mg, Final mean: 17.2 mg D: 4 wks	Grp1-Grp2: -1.3 p: 0.005			
Chien, 2007[24]	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1680 mg; Start: 5mg, Max: 10 mg, Final mean: 8.4 mg D: 4 wks	Grp1-Grp2: -1.34 p: 0.002			
Comaschi 2007[25]	Grp1: Metformin + sulfonylurea Varied, HbA1c: 7.50% Start: 400 mg, Max: 3g; Start: 2.5 mg D: 22 wks Grp2: Pioglitazone + sulfonylurea Varied, HbA1c: 7.50%; Varied Start: 15 mg, Max: 30 mg; Unclear	Grp1 F-B: -1.29 p: 0.192 Grp2 F-B: -1.29 p: <0.001 Grp1-Grp2: 0.01 (SE: 0.27) p: 0.975			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	D: 22 wks; NR				
Comaschi, 2007[25]	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: NR; 22 wks Grp2: Metformin + sulfonylurea Varied, HbA1c: 7.50% Start: 400 mg, Max: 3 g; Start: 2.5 mg D: 22 wks	Grp1 F-B: -0.99 p: <0.001 Grp2 F-B: -1.29 p: 0.192 Grp1-Grp2: 0.31 p: 0.054			
Comaschi, 2007[25]	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: 22 wks Grp2: Pioglitazone + sulfonylurea Varied, HbA1c: 7.50%; Varied, NR Start: 15 mg, Max: 30 mg; Unclear D: 22 wks;	Grp1 F-B: -0.99 p: <0.001 Grp2 F-B: -1.29 p: <0.001 Grp1-Grp2: 0.3 p: 0.043			
Davies, 2007[26]	Grp1: Metformin + NPH Varied NR; Start: 10, Mean: 0.58 IU/kg D: NR Grp2: Metformin + BHI 70/30 Varied NR; Start: 10 IU, Mean: 0.63 IU/kg D: NR	Grp1 B: 10 (2.2) F: 9.2 (1.4) F-B: -0.8 Grp2 B: 9 (1.1) F: 7.9 (1.1) F-B: -1.1 Grp1-Grp2: 0.3	Grp1-Grp2: 0.7		
DeFronzo, 1995[27]	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Glyburide Varied Start: 5 mg bid, Max: 10 mg bid	Grp1 B: 8.9 F: 8.5 F-B: -0.4 (SE: 0.1) Grp2 B: 8.5 F: 8.7 F-B: 0.2 (SE: 0.1) Grp1-Grp2: -0.6 p: <0.001	Grp1 B: 92.6 (14.5) F: 87.8 F-B: -3.8 (SE: 0.2) p: <0.001 Grp2 F-B: -0.3 (SE: 0.2) p: NS Grp1-Grp2: -3.5		
DeFronzo, 1995[27]	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg	Grp1 B: 8.9 F: 8.5	Grp1 F-B: -3.8 (SE: 0.2) p: <0.001		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2500 mg; Start: 10 mg, Max: 20 mg	F-B: -0.4 (SE: 0.1) Grp2 B: 8.8 F: 7.1 F-B: -1.7 (SE: 0.1) Grp1-Grp2: 1.3 p: <0.001	Grp2 F-B: 0.4 (SE: 0.2) p: NS Grp1-Grp2: -4.2		
DeFronzo, 2005[28]	Grp1: Metformin + placebo Fixed >=1500 mg/d Grp2: Metformin + exenatide Fixed >=1500 mg/d Fixed 10 mcg	Grp1: B: 8.2 (0.1) F: NR Grp2: B: 8.26 (0.11) F: NR	Grp1: B: 100 (19) F: NR Grp2: B: 100 (22) F: NR	Grp1: B: NR F: NR Grp2: B: NR F: NR	Grp1: B: NR F: NR Grp2: B: NR F: NR
DeFronzo, 2005[28]	Grp1: Metformin + placebo Fixed >=1500 mg/d Grp2: Metformin + exenatide Fixed >=1500 mg/d Fixed 20 mcg	Grp1: B: 8.2 (0.1) F: NR Grp2: B: 8.18 (0.09) F: NR	Grp1: B: 100 (19) F: NR Grp2: B: 101 (20) F: NR	Grp1: B: NR F: NR Grp2: B: NR F: NR	Grp1: B: NR F: NR Grp2: B: NR F: NR
DeFronzo, 2009[29]	Grp1: Metformin Fixed Grp2: Metformin + Saxagliptin Fixed NR; Mean: 2.5 mg	Grp1 F-B: Grp2 F-B: -0.59 (SE: 0.07) p: <0.0001 Grp1-Grp2: 0.73 (SE: 0.1) (CI: 0.53, 0.92) p: <0.0001			
DeFronzo, 2009[29]	Grp1: Metformin Fixed Grp2: Metformin + Saxagliptin Fixed NR; Mean: 5 mg	Grp1 F-B: 0 Grp2 F-B: -0.69 (SE: 0.07) p: <0.0001 Grp1-Grp2: 0.83 (SE: 0.1) (CI: 0.63, 1.02) p: <0.0001			
DeFronzo, 2009[29]	Grp1: Metformin Fixed Grp2: Metformin+ Saxagliptin Fixed	Grp1 F-B: 0 Grp2 F-B: -0.58 (SE: 0.07)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	NR; Mean: 10 mg	p: <0.0001 Grp1-Grp2: 0.72 (SE: 0.1) (CI: 0.52, 0.91) p: <0.0001			
Defronzo, 2010[30]	Grp1: Metformin + rosiglitazone Varied NR; Start: 4 mg, Max: 8 mg D: NR Grp2: Metformin + exenatide Varied Start: 0.010 mg, Max: 0.02 mg D: NR	Grp1 F-B: -1 (SD: 0.1) p: <0.05 Grp2 F-B: -0.9 (SD: 0.1) p: <0.05 Grp1-Grp2: -0.1 p: 0.72	Grp1 F-B: 1.5 (0.5) p: <0.05 Grp2 F-B: -2.8 (0.5) p: <0.05 Grp1-Grp2: 4.3 p: <0.001		
DeFronzo, 2012[31]	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.6) F-B: -0.1 (0.07) Grp2: B: 8.5 (0.7) F-B: -1 (0.08)	Grp1: F-B: -0.7 Grp2: F-B: -0.7		
DeFronzo, 2012[31]	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.6) F-B: -0.1 (0.07) Grp2: B: 8.6 (0.7) F-B: -0.9 (0.06)	Grp1: F-B: -0.7 Grp2: F-B: -0.02		
DeFronzo, 2012[31]	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.6) F-B: -0.1 (0.07) Grp2: B: 8.5 (0.7) F-B: -0.9 (0.1)	Grp1: F-B: -0.7		
DeFronzo,	Grp1: Metformin + placebo	Grp1:	Grp1:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2012[31]	Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) ITT: No Followup (wks): 26	B: 8.5 (0.6) F-B: -0.1 (0.07) Grp2: B: 8.5 (0.7) F-B: -0.7 (0.07)	F-B: -0.7		
DeFronzo, 2012[31]	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.6) F-B: -0.1 (0.07) Grp2: B: 8.6 (0.7) F-B: -0.7 (0.07)	Grp1: F-B: -0.7		
DeFronzo, 2012[31]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.7) F-B: -0.7 (0.07) Grp2: B: 8.6 (0.7) F-B: -0.7 (0.07)	Grp2: F-B: -0.02		
DeFronzo, 2012[31]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.7) F-B: -0.7 (0.07) Grp2: B: 8.6 (0.7) F-B: -0.9 (0.06)	Grp2: F-B: -0.7		
DeFronzo, 2012[31]	Grp1: Metformin + pioglitazone + placebo	Grp1: B: 8.5 (0.7)	Grp2: F-B: -0.7		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: No Followup (wks): 26	F-B: -0.9 (0.1) Grp2: B: 8.6 (0.7) F-B: -0.9 (0.06)			
DeFronzo, 2012[31]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.7) F-B: -0.9 (0.1) Grp2: B: 8.6 (0.7) F-B: -0.7 (0.07)	Grp2: F-B: -0.02		
DeFronzo, 2012[31]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.7) F-B: -1 (0.08) Grp2: B: 8.6 (0.7) F-B: -0.9 (0.06)	Grp2: F-B: -0.02		
DeFronzo, 2012[31]	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): 26	Grp1: B: 8.5 (0.7) F-B: -1 (0.08) Grp2: B: 8.6 (0.7) F-B: -0.7 (0.07)	Grp2: F-B: -0.7		
Del Prato, 2015[32]	Grp1: Metformin + glipizide Titrated 5,10,20mg Grp2: Metformin + dapagliflozin Titrated 2,5,10mg ITT: No	Grp1: B: 7.74 (0.89) F-B: NR Grp2: B: 7.69 (0.86)	Grp1: B: 87.6 (17) F-B: NR Grp2: B: 88.4 (16.3)	Grp1: B: 133.8 (14.7) F-B: NR Grp2: B: 132.8 (14.9)	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Followup (wks): 208	F-B: NR	F-B: NR	F-B: NR	
Del Prato, 2014[33]	Grp1: Metformin + glipizide Titrated 1823.4 mg Titrated 5 mg Grp2: Metformin + alopgliptin Titrated 1825.2 mg mg Fixed 12.5 mg	Grp1: B: 7.6 (0.62) F: NR Grp2: B: 7.6 (0.6) F: NR	Grp1: B: 85.6 (18.52) F: NR Grp2: B: 85.3 (18.96) F: NR		
Del Prato, 2014[33]	Grp1: Metformin + glipizide Titrated 1823.4 mg Titrated 5 mg Grp2: Metformin + alopgliptin Titrated 1837.2 mg Fixed 25 mg	Grp1: B: 7.6 (0.62) F: NR Grp2: B: 7.6 (0.61) F: NR	Grp1: B: 85.6 (18.52) F: NR Grp2: B: 86.3 (19.33) F: NR		
Derosa, 2004[34]	Grp1: Metformin Varied Start: 1000 mg, Max: 1000 mg tid Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg bid	Grp1 B: 8.4 (1.0) F: 7 (0.9) F-B: -1.4 (CI: -5.7, -0.51) p: 0.01 Grp2 B: 8.5 (1.2) F: 6.9 (0.7) F-B: -1.6 (CI: -6.4, -0.47) p: 0.01 Grp1-Grp2: 0.2			
Derosa, 2005[35]	Grp1: Metformin + rosiglitazone Fixed Start: 500 mg tid; Start: 2 mg Grp2: Metformin + glimepiride Fixed Start: 500mg tid; Start: 4mg qday		Grp1 B: 74.2 (3.6) F: 68.3 (3) p: <0.01 F-B: -5.9 Grp2 B: 75.6 (4.2) F: 71.1 (3.2) p: <0.05 F-B: -4.5 Grp1-Grp2: -1.4		
Derosa, 2005[36]	Grp1: Metformin + rosiglitazone Fixed Start: 500 mg tid, Max: 500 mg tid; Start: 4 mg, Max: 4 mg	Grp1 B: 8 (0.7) F: 6.8 (0.6) p: <0.01 F-B: -1.2			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Metformin + glimepiride Fixed Start: 500 mg tid, Max: 500 mg tid; Start: 2 mg, Max: 2 mg	Grp2 B: 7.9 (0.6) F: 7 (0.7) p: <0.05 F-B: -0.9 Grp1-Grp2: -0.3 (SE: 0.23)			
Derosa, 2009[38]	Grp1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos Grp2: Pioglitazone Varied Start: 15 mg, Max: 45 mg D: 3 mos	Grp1 B: 9.1 (1.2) F: 7.9 (0.5) p: <0.01 F-B: -1.1 (0.5) p: <0.01 Grp2 B: 9.2 (1.3) F: 8.2 (0.7) p: <0.01 F-B: -1 (0.7) p: <0.01 Grp1-Grp2: -0.1 (SE: 0.33)			
Derosa, 2009[38]	Grp1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos Grp2: Metformin + pioglitazone Varied, prespecified target dose Start: 850 mg, Max: 2550 mg; Start: 15 mg, Max: 45 mg D: 3 mos	Grp1 B: 9.1 (1.2) F: 7.9 (0.5) p: <0.01 F-B: -1.1 (0.5) p: <0.01 Grp2 B: 9.3 (1.4) F: 7.2 (0.3) p: >0.001 F-B: -2.1 (0.3) p: <0.01 Grp1-Grp2: 1.0 (SE: 0.27)	BMI Grp1 B: 27.2 (1.5) F: 26.7 (1.2) F-B: -1.8% Grp2 B: 27.4 (1.6) F: 26.9 (1.3) F-B: -1.8% Grp1-Grp2: 0		
Derosa, 2009[38]	Grp1: Metformin Varied, prespecified target dose Start: 1000 mg, Max: 3000 mg D: 3 mos Grp2: Metformin + glimepiride Fixed Start: 850 mg, Max: 850 mg; Start: 2 mg, Max: 6 mg D: NR; 3 mos	Grp1 B: 9.1 (1.2) F: 7.9 (0.5) F-B: -1.1 (0.5) p: <0.01 Grp2 B: 9 (1.1) F: 7.8 (0.4) F-B: -1.2 (0.4) p: <0.01 Grp1-Grp2: 0.1 (SE: 0.29)	BMI Grp1 B: 27.2 (1.5) F: 26.7 (1.2) F-B: -1.8% Grp2 B: 27.1 (1.4) F: 28.4 (2.2) F-B: 4.8% p: <0.05 Grp1-Grp2: -1.8		
Derosa,	Grp1: Metformin + Pioglitazone	Grp1			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2009[38]	Varied, prespecified target dose Start: 850 mg, Max: 2550 mg; Start: 15 mg, Max: 45 mg D: 3 mos Grp2: Metformin + glimepiride Fixed; Varied, prespecified target dose Start: 850 mg, Max: 850 mg; Start: 2 mg, Max: 6 mg D: NA; 3 mos	B: 9.3 (1.4) F: 7.2 (0.3) p: >0.001 F-B: -2.1 (0.3) p: <0.01 Grp2 B: 9 (1.1) F: 7.8 (0.4) p: <0.01 F-B: -1.2 (0.4) p: <0.01 Grp1-Grp2: -0.9 (SE: 0.25)			
Derosa, 2010[39]	Grp1: Metformin + glibenclamide Mean: 1500 mg; Start: 7.5 mg, Max: 15 mg D: NR Grp2: Metformin + exenatide NR NR; Start: 10 mcg, Max: 20 mcg D: NR	Grp1 B: 8.9 (0.8) F: 7.1 (0.2) p:NS F-B: -1.8 p: <0.001 Grp2 B: 8.8 (0.7) F: 7.3 (0.3) F-B: -1.5 p: <0.001 Grp1-Grp2: -0.3 p: NS	Grp1 B: 82.4 (9.1) F: 86.7 (11.2) p: <0.05 F-B: 4.3 p: <0.05 Grp2 B: 82 (8.3) F: 74 (4.1) F-B: -8 p: <0.001 Grp1-Grp2: 12.3		
Derosa, 2011[40]	Grp1: Metformin + glimepiride Not specified Titrated (Max: 2mg tidstart 1mg tid) Grp2: Metformin + exenatide Not specified Titrated (Max: 10 ug bidstart 5 ug bid) ITT: No Followup (wks): 48	Grp1: B: 8.8 (0.8) F: 7.4 (0.2) F-B:p <0.01 Grp2: B: 8.7 (0.7) F: 7.5 (0.3) F-B:p <0.01 Between-group difference: p NS	Grp1: B: 81.4 (8.1) F: 80.5 (7.7) F-B:p >0.05 Grp2: B: 80.2 (7.5) F: 75.1 (6.5) F-B:p <0.001		
Derosa, 2012[41]	Grp1: Metformin + placebo Titrated (Mean: 2500 mg) Grp2: Metformin + sitagliptin Titrated (Mean: 2500 mg) Fixed (100mg daily) ITT: No Followup (wks): 48	Grp1: B: 8 (0.7) F: 7.3 (0.2) F-B:p <0.01 Grp2: B: 8.1 (0.8) F: 6.7 (0.1) F-B:p <0.001 Between-group difference:	Grp1: B: 78.6 (6.7) F: 76.3 (5.2) F-B:p <0.05 Grp2: B: 78.4 (6.6) F: 75.9 (5) F-B:p <0.05		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		p <0.05			
Derosa, 2013[42]	Grp1: Metformin + placebo Fixed (2500+/-500mg/day as previously determined during run-in period) Grp2: Metformin + sitagliptin Fixed (2500+/-500mg/day as previously determined during run-in period) Fixed (100mg) ITT: No Followup (wks): 48	Grp1: B: 8 (0.7) F: 7.3 (0.2) p<0.05 F-B:p <0.01 Grp2: B: 8.1 (0.8) F: 6.7 (0.1) F-B:p <0.001	Grp1: B: 78.6 (6.7) F: 76.3 (5.2) F-B:p <0.05 Grp2: B: 78.4 (6.6) F: 75.9 (5) F-B:p <0.05		
Derosa, 2013[43]	Grp1: Metformin + placebo Fixed (Mean: 2500 +/- 500mg titrated up during run-in for 8+/- 2 months) Grp2: Metformin + exenatide Fixed (Mean: 2500 +/- 500mg titrated up during run-in over 8+/- 2 months) Titrated (Max: 20 ug daily5ug b.i.d. for the first 4 wks and then 10 ug b.i.d. thereafter) ITT: No Followup (wks): 48	Grp1: B: 7.9 (0.6) F: 7.5 (0.3) F-B:p <0.01 Grp2: B: 8.1 (0.8) F: 6.9 (0.2) F-B:p <0.001 Between-group difference: p <0.05	Grp1: B: 90.5 (10.3) F: 88.2 (8.9) F-B:p <0.05 Grp2: B: 89 (9.7) F: 82.6 (5.2) F-B:p <0.001 Between-group difference: p <0.01	Grp1: B: 131.6 (6.1) F: 128.6 (5) F-B:p >0.05 Grp2: B: 132.5 (7.4) F: 125.7 (4.1) F-B:p <0.05 Between-group difference: p not statistically significant	
Diamant, 2010[44]	Grp1: Metformin + exenatide Not specified Fixed (2mg weekly) Grp2: Metformin + insulin glargine Not specified Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT: No Followup (wks): 26	Grp1: F-B: -1.5 (0.06) Grp2: F-B: -1.4 (0.07) Between-group difference: Grp1: -0.18 0.08 (-0.34-0.02) p 0.031	Grp1: F-B: -3.2 Grp2: F-B: 1.1 Between-group difference: Grp1: -4.4 (-5--3.6)		
Diamant, 2010[44]	Grp1: Metformin + exenatide Not specified Fixed (2mg weekly) Grp2: Metformin + insulin glargine Not specified Titrated (started at 10 IU per day but adjusted by patient to keep glucose at	Grp1: F-B: -1.5 Grp2: F-B: -1.4 Between-group difference: Grp1: -0.18 0.08 (-	Grp1: F-B: -2.5 (0.3) Grp2: F-B: 2.2 (0.3) Between-group difference: Grp1: -4.7 0.4 (-5.4--4)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	4-5.5mmol/L) ITT: No Followup (wks): 26	0.34-0.02) p 0.031	p <0.001 p		
Einhorn, 2000[45]	Grp1: Metformin NR Grp2: Metformin + pioglitazone NR; Fixed NR; Start: 30 mg	Grp1 B: 9.75 (SE: 1.3) F-B: p: <0.05 Grp2 B: 9.86 (SE: 1.4) F-B: p: <0.05 Grp1-Grp2: -0.83 p: <0.05	Grp1 F-B: -1.36 Grp2 F-B: 0.95 Grp1-Grp2: -2.31		
Erdem, 2008[46]	Grp1: Metformin Varied, glucose: 110 mg/dL Start: 1000 mg, Max: 2000 mg D: every 2 wks until goal Grp2: Pioglitazone Varied, glucose: 110 mg/dL Start: 15 mg, Max: 45 mg D: every 2 wks until goal	Grp1 B: 6.74 (1.3) F: 6.15 (0.53) p: 0.02 F-B: -0.59 Grp2 B: 6.34 (1.2) p: 0.31 F: 5.6 (0.7) p: 0.01 F-B: -0.74 Grp1-Grp2: 0.15 (SE: 0.50)			
Erem, 2014[47]	Grp1: Metformin Titrated (Max: 2000mg4-8 wks of titration then fixed after that - article reported all patients ended up on 2000 mg) Grp2: Pioglitazone Titrated (Max: 45mg according to glycemic controlinitiated at 15mg/day and titrated in first 4-8 wks then fixed after that (ended up 6 pts on 15 mg, 12 pts on 30 mg and 1 pt on 45 mg)) ITT: No Followup (wks): 48	Grp1: B: 7.62 (1.06) F: 6.4 (0.7) F-B:p 0.001 Grp2: B: 8.03 (1.7) F: 6.46 (0.56) F-B:p 0.033			
Esposito, 2011[48]	Grp1: Metformin Titrated (Max: 1000mg twice dailyend of titration: 36% on 1500 mg/d and 64% on 2000 mg/d) Grp2: Pioglitazone + pioglitazone	Grp1: B: 8.1 (1) F-B: -0.9 (0.5) Grp2: B: 8 (1)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Titrated (Max: 45 mgend of titration period: 27% on 30 mg/d and 72% on 45 mg/d) Titrated (Max: 30-45mg daily) ITT: Yes Followup (wks): 24	F-B: -0.9 (0.5) Between-group difference: Grp1: 0 (-0.3-0.3)			
Esteghamati, 2014[49]	Grp1: Metformin Fixed (1000mg) Grp2: Pioglitazone Fixed (30mg) ITT: No Followup (wks): 12	Grp1: B: 66 (12.8) F: 57 (15.5) F-B: -9.1 (-12.6-5.6) p <0.001 Grp2: B: 65 (16.5) F: 57 (17.7) F-B: -7.9 (-12.2-3.5) p 0.001	Grp1: B: 74.34 (12.81) F: 74.49 (12.31) F-B: 0.15 (-0.86-0.56) p 0.672 Grp2: B: 77.01 (13.61) F: 77.74 (14.73) F-B: 0.18 (-0.84-1.21) p 0.258		
Esteghamati, 2015[50]	Grp1: Metformin Fixed 1000 mg/d Grp2: Metformin + piogltazone Fixed 30 mg/d	Grp1: B: 8.4 (0.25) F-B: 7.46 (0.21) Grp2: B: 8.06 (0.21) F-B: 6.95 (0.16)	Grp1: B: 78.5 (2.07) F-B: 77.82 (2.06) Grp2: B: 75.36 (1.61) F-B: 76.73 (1.7)		
Feinglos, 2005[52]	Grp1: Metformin Fixed Start: at least 1000 mg Grp2: Metformin + glipizide Fixed Start: at least 1000 mg; Start: 2.5 mg	Grp1 B: 7.64 F: 7.46 (SE: 0.1) F-B: -0.19 Grp2 B: 7.45 F: 6.8 (SE: 0.1) F-B: -0.66 Grp1-Grp2: 0.47 p: <0.0002	Grp1 B: 90.8 (18.4) F: 89.1 F-B: -1.7 Grp2 B: 90 (18.7) F: 90.4 F-B: 0.4 Grp1-Grp2: -2.1 p: < 0.0001		
Ferrannini, 2013[53]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2: Empagliflozin Fixed (10 mg)	Grp1: B: 8.15 F-B: -0.56 (-0.79-0.33) p Grp2: B: 7.88 F-B: -0.34 (-0.54-	Grp1: B: 85.8 F-B: -1.3 (-2.3--0.3) p Grp2: B: 83.5 F-B: -2.6 (-3.5--1.8)	Grp1: B: 131.7 F-B: 2 (-1.8-5.7) p Grp2: B: 131.9 F-B: -1.7 (-4.9-1.6)	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		0.14)			
	ITT: No Followup (wks): 90				
Ferrannini, 2013[53]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2: Metformin + empagliflozin Not specified Fixed (25 mg) ITT: No Followup (wks): 90	Grp1: B: 8.15 F-B: -0.56 (-0.79-0.33) Grp2: B: 7.89 F-B: -0.63 (-0.76-0.5)	Grp1: B: 85.8 F-B: -1.3 (-2.3--0.3) Grp2: B: 83.5 F-B: -2.6 (-3.5--1.8)	Grp1: B: 131.7 F-B: 2 (-1.8-5.7) Grp2: B: 131.9 F-B: -1.7 (-4.9-1.6)	
Ferrannini, 2013[53]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2: Metformin + empagliflozin Not specified Fixed (10 mg) ITT: No Followup (wks): 90	Grp1: B: 8.15 F-B: -0.56 (-0.79-0.33) Grp2: B: 7.92 F-B: -0.34 (-0.47-0.21)	Grp1: B: 85.8 F-B: -1.3 (-2.3--0.3) Grp2: B: 88.6 F-B: -0.4 (-1.5-0.7)	Grp1: B: 131.7 F-B: 2 (-1.8-5.7) Grp2: B: 137.4 F-B: 1.8 (-1.5-5.2)	
Ferrannini, 2013[53]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2: Empagliflozin Fixed (25 mg) ITT: No Followup (wks): 90	Grp1: B: 8.15 F-B: -0.56 (-0.79-0.33) Grp2: B: 7.99 F-B: -0.47 (-0.66-0.27)	Grp1: B: 85.8 F-B: -1.3 (-2.3--0.3) Grp2: B: 90.7 F-B: -3.1 (-3.9--2.4)	Grp1: B: 131.7 F-B: 2 (-1.8-5.7) Grp2: B: 134.5 F-B: -3 (-5.3-0.6)	
Ferrannini, 2013[53]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2: Empagliflozin Fixed (25mg) ITT: No Followup (wks): 90	Grp1: B: 8.15 F-B: -0.56 (-0.79-0.33) Grp2: B: 7.99 F-B: -0.47 (-0.66-0.27)	Grp1: B: 85.8 F-B: -1.3 (-2.3--0.3) Grp2: B: 89.7 F-B: -4 (-4.8--3.3)	Grp1: B: 131.7 F-B: 2 (-1.8-5.7) Grp2: B: 131.6 F-B: 0.1 (-3.2-3.4)	
Ferrannini, 2013[53]	Grp1: Metformin Fixed (Max: maximum of 1,000 mg	Grp1: B: 8.15	Grp1: B: 85.8	Grp1: B: 131.7	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	twice daily or the maximum tolerated dose) Grp2: Metformin + sitagliptin Not specified Fixed (100 mg) ITT: No Followup (wks): 90	F-B: -0.56 (-0.79-0.33) Grp2: B: 8.03 F-B: -0.4 (-0.6-0.2)	F-B: -1.3 (-2.3--0.3) Grp2: B: 83.4 F-B: -2.2 (-3.1--1.4)	F-B: 2 (-1.8-5.7) Grp2: B: 133.9 F-B: -3.3 (-5.7-0.9)	
Ferrannini, 2013[53]	Grp1: Empagliflozin Fixed (10 mg) Grp2: Metformin + empagliflozin Not specified Fixed (25 mg) ITT: No Followup (wks): 90	Grp1: B: 7.88 F-B: -0.34 (-0.54-0.14) Grp2: B: 7.89 F-B: -0.63 (-0.76-0.5)	Grp1: B: 83.4 F-B: -2.2 (-3.1--1.4) Grp2: B: 90.7 F-B: -3.1 (-3.9--2.4)	Grp1: B: 131.6 F-B: 0.1 (-3.2-3.4) Grp2: B: 134.5 F-B: -3 (-5.3-0.6)	
Ferrannini, 2013[53]	Grp1: Empagliflozin Fixed (10 mg) Grp2: Metformin + empagliflozin Not specified Fixed (10 mg) ITT: No Followup (wks): 90	Grp1: B: 7.88 F-B: -0.34 (-0.54-0.14) Grp2: B: 7.92 F-B: -0.34 (-0.47-0.21)	Grp1: B: 83.4 F-B: -2.2 (-3.1--1.4) Grp2: B: 89.7 F-B: -4 (-4.8--3.3)	Grp1: B: 131.6 F-B: 0.1 (-3.2-3.4) Grp2: B: 137.4 F-B: 1.8 (-1.5-5.2)	
Ferrannini, 2013[53]	Grp1: Empagliflozin Fixed (10 mg) Grp2: Metformin + sitagliptin Not specified Fixed (100 mg) ITT: No Followup (wks): 90	Grp1: B: 7.88 F-B: -0.34 (-0.54-0.14) Grp2: B: 8.03 F-B: -0.4 (-0.6-0.2)	Grp1: B: 83.4 F-B: -2.2 (-3.1--1.4) Grp2: B: 88.6 F-B: -0.4 (-1.5-0.7)	Grp1: B: 131.6 F-B: 0.1 (-3.2-3.4) Grp2: B: 133.9 F-B: -3.3 (-5.7-0.9)	
Ferrannini, 2013[53]	Grp1: Empagliflozin Fixed (25mg) Grp2: Metformin + empagliflozin Not specified Fixed (25 mg) ITT: No Followup (wks): 90	Grp1: B: 7.99 F-B: -0.47 (-0.66-0.27) Grp2: B: 7.89 F-B: -0.63 (-0.76-0.5)	Grp1: B: 83.5 F-B: -2.6 (-3.5--1.8) Grp2: B: 88.6 F-B: -0.4 (-1.5-0.7)	Grp1: B: 131.9 F-B: -1.7 (-4.9-1.6) Grp2: B: 133.9 F-B: -3.3 (-5.7-0.9)	
Ferrannini, 2013[53]	Grp1: Empagliflozin Fixed (25mg) Grp2: Metformin + sitagliptin	Grp1: B: 7.99 F-B: -0.47 (-0.66-	Grp1: B: 83.5 F-B: -2.6 (-3.5--1.8)	Grp1: B: 131.9 F-B: -1.7 (-4.9-1.6)	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Not specified Fixed (100 mg) ITT: No Followup (wks): 90	0.27) Grp2: B: 8.03 F-B: -0.4 (-0.6-0.2)	Grp2: B: 89.7 F-B: -4 (-4.8--3.3)	Grp2: B: 134.5 F-B: -3 (-5.3-0.6)	
Ferrannini, 2013[53]	Grp1: Empagliflozin Fixed (25 mg) Grp2: Metformin + empagliflozin Not specified Fixed (25 mg) ITT: No Followup (wks): 90	Grp1: B: 7.99 F-B: -0.47 (-0.66-0.27) Grp2: B: 7.89 F-B: -0.63 (-0.76-0.5)	Grp1: B: 83.5 F-B: -2.6 (-3.5--1.8) Grp2: B: 90.7 F-B: -3.1 (-3.9--2.4)	Grp1: B: 131.9 F-B: -1.7 (-4.9-1.6) Grp2: B: 137.4 F-B: 1.8 (-1.5-5.2)	
Ferrannini, 2013[53]	Grp1: Empagliflozin Fixed (25mg) Grp2: Metformin + empagliflozin Not specified Fixed (10 mg) ITT: No Followup (wks): 90	Grp1: B: 7.99 F-B: -0.47 (-0.66-0.27) Grp2: B: 7.92 F-B: -0.34 (-0.47-0.21)	Grp1: B: 83.5 F-B: -2.6 (-3.5--1.8) Grp2: B: 89.7 F-B: -4 (-4.8--3.3)	Grp1: B: 131.9 F-B: -1.7 (-4.9-1.6) Grp2: B: 134.5 F-B: -3 (-5.3-0.6)	
Ferrannini, 2013[53]	Grp1: Empagliflozin Fixed (25 mg) Grp2: Metformin + empagliflozin Not specified Fixed (10 mg) ITT: No Followup (wks): 90	Grp1: B: 7.99 F-B: -0.47 (-0.66-0.27) p Grp2: B: 7.92 F-B: -0.34 (-0.47-0.21)	Grp1: B: 83.5 F-B: -2.6 (-3.5--1.8) Grp2: B: 88.6 F-B: -0.4 (-1.5-0.7)	Grp1: B: 131.9 F-B: -1.7 (-4.9-1.6) Grp2: B: 133.9 F-B: -3.3 (-5.7-0.9)	
Ferrannini, 2013[53]	Grp1: Empagliflozin Fixed (25 mg) Grp2: Metformin + sitagliptin Not specified Fixed (100 mg) ITT: No Followup (wks): 90	Grp1: B: 7.99 F-B: -0.47 (-0.66-0.27) p Grp2: B: 8.03 F-B: -0.4 (-0.6-0.2)	Grp1: B: 83.5 F-B: -2.6 (-3.5--1.8) p Grp2: B: 90.7 F-B: -3.1 (-3.9--2.4)	Grp1: B: 131.9 F-B: -1.7 (-4.9-1.6) p Grp2: B: 137.4 F-B: 1.8 (-1.5-5.2)	
Ferrannini, 2013[53]	Grp1: Metformin + sitagliptin Not specified Fixed (100 mg) Grp2: Metformin + empagliflozin Not specified	Grp1: B: 8.03 F-B: -0.4 (-0.6-0.2) Grp2: B: 7.89	Grp1: B: 88.6 F-B: -0.4 (-1.5-0.7) Grp2: B: 89.7	Grp1: B: 137.4 F-B: 1.8 (-1.5-5.2) Grp2: B: 134.5	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (25 mg) ITT: No Followup (wks): 90	F-B: -0.63 (-0.76-0.5)	F-B: -4 (-4.8--3.3)	F-B: -3 (-5.3-0.6)	
Ferrannini, 2013[53]	Grp1: Metformin + sitagliptin Not specified Fixed (100 mg) Grp2: Metformin + empagliflozin Not specified Fixed (10 mg) ITT: No Followup (wks): 90	Grp1: B: 8.03 F-B: -0.4 (-0.6-0.2) Grp2: B: 7.92 F-B: -0.34 (-0.47-0.21)	Grp1: B: 88.6 F-B: -0.4 (-1.5-0.7) Grp2: B: 90.7 F-B: -3.1 (-3.9--2.4)	Grp1: B: 137.4 F-B: 1.8 (-1.5-5.2) Grp2: B: 133.9 F-B: -3.3 (-5.7-0.9)	
Fidan, 2011[54]	Grp1: Metformin Fixed (Max: 1700 mgtitrated after rz but before observational period - from 850 mg/d up to 850mg tid up at 10 days intervals) Grp2: Rosiglitazone Fixed (Max: 8 mgtitrated after rz but before 12-wk observational period - from 4 to 8 mg/d) ITT: NR Followup (wks): 12	Grp1: B: 7.8 (0.9) F: 6.6 (1) F-B:p <0.05 Grp2: B: 7.9 (0.8) F: 6.9 (1) p>0.05 F-B:p <0.05			
Fonseca, 2000[55]	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 8 mg	Grp1 B: 8.6 (1.3) F: 9.05 F-B: 0.45 Grp2 B: 8.9 (1.5) F: 8.12 F-B: -0.78 Grp1-Grp2: 1.2 p: <0.001	Grp1 F-B: -1.2 Grp2 F-B: 0.7 Grp1-Grp2: -1.9 p: 0.0001		
Fonseca, 2000[55]	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 4 mg	Grp1 B: 8.6 (1.3) F: 9.05 F-B: 0.45 Grp2 B: 8.9 (1.3) F: 8.34	Grp1 F-B: -1.2 Grp2 F-B: 1.9 Grp1-Grp2: -3.1 p: 0.0001		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		F-B: -0.56 Grp1-Grp2: -1 p: <0.001			
Fonseca, 2012[56]	Grp1: Metformin Titrated (Max: 2000 mg/duptitration from 1500 to 2000 mg/d) Grp2: Metformin + saxagliptin Fixed (1500 mg/d) Fixed (5mg/d) ITT: No Followup (wks): 18	Grp1: B: 8.28 (0.077) F: 7.9 (0.1) F-B: -0.35 (0.081) Grp2: B: 8.41 (0.076) F: 7.5 (0.1) F-B: -0.88 (0.076) Between-group difference: Grp2: -0.52 (-0.73-0.31) p <0.001	Between-group difference: Grp1: -0.5 (-0.88--0.12) Grp2: 0.4 (-0.07-0.82)		
Forst, 2010[57]	Grp1: Metformin + placebo Fixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2: Metformin + glimepiride Fixed Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) ITT: No Followup (wks): 12	Grp1: B: 8.4 (0.7) F-B: 0.25 (0.1) Grp2: B: 8.2 (0.7) F-B: -0.68 Between-group difference: Grp2: -0.9 p <0.0001	Grp1: B: 93.1 (16.8) F-B: -0.84 Grp2: B: 90.5 (15) F-B: 0.73		
Forst, 2010[57]	Grp1: Metformin + placebo Fixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2: Metformin + linagliptin Fixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT: No Followup (wks): 12	Grp1: B: 8.4 (0.7) F-B: 0.25 (0.1) Grp2: B: 8.5 (0.8) F-B: -0.48 (0.14) Between-group difference: Grp2: -0.75 (-1.02-0.48) p <0.001	Grp1: B: 93.1 (16.8) F-B: -0.84 Grp2: B: 90.7 (14.2) F-B: -0.57		
Forst, 2010[57]	Grp1: Metformin + glimepiride Fixed Titrated (Max: 3 mgstarted from 1mg for	Grp1: B: 8.2 (0.7) F-B: -0.68	Grp1: B: 90.5 (15) F-B: 0.73		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) Grp2: Metformin + linagliptin Fixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT: No Followup (wks): 12	Grp2: B: 8.5 (0.8) F-B: -0.48 (0.14) Between-group difference: Grp1: -0.9 p <0.0001 Grp2: -0.75 (-1.02-0.48) p <0.001	Grp2: B: 90.7 (14.2) F-B: -0.57		
Forst, 2012[58]	Grp1: Metformin Not specified Grp2: Metformin + liraglutide Not specified Titrated (Max: 1.8 mg/dstarted at 0.6 mg/day and increased to max by 6 wks) ITT: No Followup (wks): 12	Grp1: B: 6.36 (0.37) F: 6.32 (0.29) Grp2: B: 6.32 (0.37) F: 5.77 (0.3) p<0.05 F-B:p <0.05	Grp1: B: 96.9 (17.5) F: 96.7 (18) F-B:p Grp2: B: 93.2 (17.1) F: 89.7 (16.6) p<0.05 F-B:p <0.05	Grp1: B: 129 (12) F: 128 (13) F-B:p Grp2: B: 131 (12) F: 128 (12) F-B:p	
Forst, 2014[59]	Grp1: Metformin + glimepiride Not specified Titrated (individually titrated in the range of 1-4mg to achieve best possible glycemic control as judged by the investigator) Grp2: Metformin + linagliptin Not specified Fixed (5mg) ITT: Yes Followup (wks): 12	Grp1: B: 57.7 (7.1) F-B: -8.2 (5.1) p <0.0001 Grp2: B: 56.8 (6.9) F-B: -6 (6) p <0.0001 Between-group difference: p NS	Grp1: B: 95.1 (21.7) F-B: 0.7 (2.5) Grp2: B: 89.6 (13.6) F-B: -1.2 (1.7)		
Gallwitz, 2011[60]	Grp1: Metformin + exenatide Fixed (Median: 2000mgcontinued at prestudy dose) Titrated (Max: 20 micrograms/daystart 5ugBID 4 w then 10ug) Grp2: Metformin + insulin aspart 70/30 Not specified Titrated (Mean: 28.4 IU/dayto reach glucose target of 5.0 -7.2 mmol/L;	Grp1: F-B: -1 Grp2: F-B: -1.14 Between-group difference: Grp1: 0.14 (-0.003-0.291)	Grp1: F-B: -4.1 (0.22) Grp2: F-B: 1 (0.22) Between-group difference: p <0.001		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	titrated "without a structured insulin dosing algorithm") ITT: No Followup (wks):				
Gallwitz, 2012[61]	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: No Followup (wks): 104	Grp1: B: 7.69 (0.03) F-B: -0.36 (0.03) Grp2: B: 7.69 (0.03) F-B: -0.16 (0.03) Between-group difference: Grp2: 0.2 0.05 (0.09-0.3) p 0.0004	Grp1: B: 87 (0.6) F-B: 1.3 (0.2) Grp2: B: 86 (0.7) F-B: -1.4 (0.2) Between-group difference: Grp2: -2.7 (-3.2--2.2) p <0.0001		
Garber, 2002[63]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.26 (1.08) F: 7.23 F-B: -1.03 Grp2 B: 8.21 (1.09) F: 6.97 F-B: -1.24 Grp1-Grp2: 0.21	Grp1 F-B: -0.6 p: <0.05 Grp2 F-B: 1.7 Grp1-Grp2: 2.3		
Garber, 2002[63]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.26 (1.08) F: 7.23 F-B: -1.03 Grp2 B: 8.18 (1.14) F: 6.65 F-B: -1.53 Grp1-Grp2: 0.5 p: <0.001	Grp1 F-B: -0.6 Grp2 F-B: 1.4 p: <0.05 Grp1-Grp2: -2		
Garber, 2002[63]	Grp1: Metformin Varied	Grp1 B: 8.26 (1.08)	Grp1 F-B: -0.6		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg, Max: 1000 mg; Start: 1.25 mg, Max: 5 mg	F: 7.23 F-B: -1.03 Grp2 B: 8.25 (1.11) F: 6.77 F-B: -1.48 Grp1-Grp2: 0.45 p: <0.001	Grp2 F-B: 1.9 p: <0.05 Grp1-Grp2: -2.5		
Garber, 2003[64]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.42 (1.4) F: 7.01 F-B: -1.53 Grp2 B: 8.67 (1.4) F: 6.75 F-B: -1.9 Grp1-Grp2: 0.37	Grp1 B: 92.8 (15.6) F: 91.7 F-B: -1.1 p: <0.001 Grp2 B: 91 (16.0) F: 93 F-B: 2 p: NS Grp1-Grp2: -3.1		
Garber, 2003[64]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg, Max: 1000 mg; Start: 1.25 mg, Max: 5 mg	Grp1 B: 8.42 (1.4) F: 7.01 F-B: -1.53 Grp2 B: 8.78 (1.5) F: 6.43 F-B: -2.27 Grp1-Grp2: -0.74 p: 0.0003	Grp1 B: 92.8 (15.6) F: 91.7 F-B: -1.1 p: <0.001 Grp2 B: 91.9 (17.4) F: 93.5 F-B: 1.6 p: NS Grp1-Grp2: -2.7		
Garber, 2006[65]	Grp1: Metformin + rosiglitazone Varied Start: 1500-2000 mg, Max: 2000 mg; Start: 4 mg, Max: 8 mg Grp2: Metformin + glibenclamide Varied Start: 1000 mg, Max: 2000 mg; Start: 5 mg, Max: 10 mg		Grp1 B: 94 F: 95.4 F-B: 1.4 Grp2 B: 92 F: 95 F-B: 3 Grp1-Grp2: -1.5 p: <0.001		
Garber, 2009[66]	Grp1: Glimepiride Varied, prespecified target dose	Grp1 F-B: 0.51 (SD: 1.2)	Grp1 F-B: 1 (0.5)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 2 mg, Max: 8 mg D: 2 Wks Grp2: Liraglutide Varied, prespecified target dose Start: 0.6 mg, Max: 1.2 mg D: 2 Wks	Grp2 F-B: 0.84 (SD: 1.23) Grp1-Grp2: 0.62 (CI: 0.42, 0.83) p<0.0001	Grp2 F-B: -2 (0.5) Grp1-Grp2: 3		
Garber, 2009[66]	Grp1: Glimepiride Varied, prespecified target dose Start: 2 mg, Max: 8 mg D: 2 Wks Grp2: Liraglutide Varied, prespecified target dose Start: 0.6 mg, Max: 1.8 mg D: 2 Wks	Grp1 F-B: 0.51 (SD: 1.2) Grp2 F-B: 1.14 (SD: 1.24) Grp1-Grp2: 0.33 (CI: 0.13, 0.53) p: 0.0014	Grp1 F-B: 1 (0.5) Grp2 F-B: -2.5 (0.5) Grp1-Grp2: 3.5		
Garber, 2011[67]	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.2 mg) ITT: Yes Followup (wks): 104	Grp1: B: 8.2 (1.1) F: 7.5 (0.15) F-B: -0.3 Grp2: B: 8.2 (1.1) F: 7.1 (0.1) F-B: -0.6 Between-group difference: Grp2: -0.31 (-0.54-0.08) p 0.0076	Grp1: B: 93.3 (19) F-B: 0.95 Grp2: B: 92.6 (20.85) F-B: -2.7 Between-group difference: Grp2: -3.65 (-4.44--2.86) p <0.0001	Grp1: B: 130 (16.1) F-B: -0.49 Grp2: B: 127.6 (14.3) F-B: -1.35 Between-group difference: Grp2: -0.86 (-3.18-1.46) p 0.46574	Grp1: F-B: 0.67 Grp2: F-B: 2.04 Grp2: 1.36 (-0.17-2.9) p 0.0821
Garber, 2011[67]	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.8 mg) ITT: Yes Followup (wks): 104	Grp1: B: 8.2 (1.1) F: 7.5 (0.15) F-B: -0.3 Grp2: B: 8.2 (1.1) F: 6.9 (0.1) F-B: -0.9 Between-group difference: Grp2: -0.6 (-0.83-0.38) p <0.0001	Grp1: B: 93.3 (19) F-B: 0.95 Grp2: B: 92.1 (19) F-B: -1.89 Between-group difference: Grp2: -2.84 (-3.63--2.06) p <0.0001	Grp1: B: 130 (16.1) F-B: -0.49 Grp2: B: 128 (13.9) F-B: -2.37 Between-group difference: Grp2: -1.88 (-4.21-0.45) p 0.1135	Grp1: F-B: 0.67 Grp2: F-B: 0.92 Between-group difference: Grp2: 0.24 (-1.3-1.78) p 0.7589
Genovese,	Grp1: Metformin + placebo	Grp1:	Grp1:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2013[68]	Fixed (2550 mg) Grp2: Metformin + pioglitazone Fixed (2550 mg) Fixed (45titrated from 30 mg to 45 mg in first four wks then fixed at 45 for 20 wks) ITT: Yes Followup (wks): 24	B: 7.02 (0.46) F: 6.96 (0.74) F-B:p Grp2: B: 6.92 (0.42) F: 6.41 (0.65) F-B:p Between-group difference: p <0.001	B: 89 (17.2) F: 87.2 (17.2) F-B:p Grp2: B: 88.8 (14) F: 89.4 (14.7) F-B:p Between-group difference: p 0.32		
Genovese, 2013[69]	Grp1: Metformin Titrated (starting dose of 850mg/day, up-titrated to 1700mg or 2550mg in later visits depending on the glycemic response) Grp2: Pioglitazone + placebo Titrated (Max: 45mgstarting dose of 30mg qd, up-titrated to 45mg qd in later visits in the case of poor response) ITT: No Followup (wks): 16	Grp1: B: 6.7 (0.7) F: 6.5 (0.7) F-B:p <0.01 Grp2: B: 6.9 (0.9) F: 6.5 (0.8) F-B:p <0.05 Between-group difference: p 0.36			
Goke, 2010[70]	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin Fixed (5 mg) ITT: No Followup (wks): 104	Grp1: B: 7.65 (0.04) F: 7.27 F-B: -0.41 (0.04) Grp2: B: 7.65 (0.04) F: 7.27 F-B: -0.35 (0.04) Between-group difference: Grp2: -0.05 0.06 (-0.17-0.06) p	Grp1: B: 88.6 (1) F-B: 1.3 (0.2) Grp2: B: 88.7 (0.9) F-B: -1.5 (0.2) Between-group difference: Grp2: -2.8 0.3 (-3.3--2.2) p		
Goldstein, 2003[71]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glipizide Fixed	Grp1 B: 8.6 (1.2) F: 8.4 (0.1) F-B: -0.2 Grp2	Grp1 B: 94.2 (16.7 F: 91.5 F-B: -2.7 (SE: 0.3) Grp2		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 15 mg bid	B: 8.9 (1.1) F: 8.5 (0.1) F-B: -0.4 Grp1-Grp2: 0.2	B: 90 (17.4) F: 89.6 F-B: -0.4 (SE: 0.3) Grp1-Grp2: -2.3		
Goldstein, 2003[71]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glipizide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	Grp1 B: 8.6 (1.2) F: 8.4 (0.1) F-B: -0.2 Grp2 B: 8.7 (1.2) F: 7.4 (0.1) F-B: -1.3 Grp1-Grp2: 1.06 p: <0.001	Grp1 B: 94.2 (16.7) F: 91.5 F-B: -2.7 (SE: 0.3) Grp2 B: 95.1 (17.8) F: 94.8 F-B: -0.3 (SE: 0.3) Grp1-Grp2: -2.4 p: <0.001		
Goldstein, 2007[72]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg D: 3 wks Grp2: Sitagliptin Varied, prespecified target dose Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -1.13 (CI: -1.29, -0.97) Grp2 F-B: -0.66 (CI: -0.83, -0.5) Grp1-Grp2: -0.47	Grp1 F-B: significant reduction relative to baseline Grp2 F-B: 0		
Goldstein, 2007[72]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 100 mg D: 1 wk Grp2: Sitagliptin Varied, prespecified target dose Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -0.82 (CI: -0.98, -0.66) Grp2 F-B: -0.66 (CI: -0.83, -0.5) Grp1-Grp2: -0.16	Grp1 F-B: significant reduction relative to baseline Grp2 F-B: 0		
Goldstein, 2007[72]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 100 mg D: 1 wk Grp2: Metformin + sitagliptin Varied, prespecified target dose Start: 500 mg, Max: 1000 mg; Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -0.82 (CI: -0.98, -0.66) Grp2 F-B: -1.4 (CI: -1.56, -1.24) Grp1-Grp2: 0.58	Grp1 F-B: significant reduction relative to baseline Grp2 F-B: significant reduction relative to baseline		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Goldstein, 2007[72]	Grp1: Metformin Varied, prespecified target dose Start: 500 mg, Max: 100 mg D: 1 wk Grp2: Metformin + sitagliptin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg; Start: 50 mg, Max: 100 mg D: 3 wks; 1wk	Grp1 F-B: -0.82 (CI: -0.98, -0.66) Grp2 F-B: -1.9 (CI: -2.06, -1.74) Grp1-Grp2: 1.08	Grp1 F-B: significant reduction relative to baseline Grp2 F-B: significant reduction relative to baseline		
Goldstein, 2007[72]	Grp1: Metformin Fixed Start: 500 mg, Max: 2000 mg D: 3 wks Grp2: Metformin + sitagliptin Varied, prespecified target dose Start: 500 mg, Max: 1000 mg; Start: 50 mg, Max: 100 mg D: 1 wk	Grp1 F-B: -1.13 (CI: -1.29, -0.97) Grp2 F-B: -1.4 (CI: -1.56, -1.24) Grp1-Grp2: 0.27	Grp1 F-B: significant reduction relative to baseline Grp2 F-B: significant reduction relative to baseline		
Goldstein, 2007[72]	Grp1: Metformin Fixed Start: 500 mg, Max: 2000 mg D: 3 wks Grp2: Metformin + sitagliptin Varied, prespecified target dose Start: 500 mg, Max: 2000 mg; Start: 50 mg, Max: 100 mg D: 3 wks; 1 wk	Grp1 F-B: -1.13 (CI: -1.29, -0.97) Grp2 F-B: -1.9 (CI: -2.06, -1.74) Grp1-Grp2: 0.77 (SE: 0.12)	Grp1 F-B: significant reduction relative to baseline Grp2 F-B: significant reduction relative to baseline		
Gomez-Perez, 2002[73]	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 2 mg bid	Grp1 B: 9.8 (SE: 0.3) F: 10.2 (SE: 0.3) F-B: 0.3 p: 0.2651 Grp2 B: 10.2 (SE: 0.2) F: 9.5 (SE: 0.3) F-B: -0.7 p: 0.052 Grp1-Grp2: 1 p: 0.0132			
Gomez-Perez,	Grp1: Metformin Fixed	Grp1 B: 9.8 (SE: 0.3)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2002[73]	Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 4 mg bid	F: 10.2 (SE: 0.3) F-B: 0.3 p: 0.2651 Grp2 B: 9.75 (SE: 0.2) F: 8.6 (SE: 0.4) F-B: -1.2 p: 0.008 Grp1-Grp2: 1.5 p: 0.0002			
Gupta, 2009[74]	Grp1: Metformin + ADA diet Varied, prespecified target dose Start: 500 mg, Max: 2000 mg D: every 1 wk increment by 500 mg Grp2: Pioglitazone + ADA diet Varied, glucose: FPG > 100 mg, HbA1c: 7.0% Start: 30 mg, Max: 45 mg D: 8 wks	Grp1 F-B: -0.24 (0.14) Grp2 F-B: -0.09 (0.13) Grp1-Grp2: -0.15 (SE: 0.22)	Grp1 F-B: -3.21 (0.7) Grp2 F-B: 2.15 (1.09) Grp1-Grp2: -5.36		
Gupta, 2009[74]	Grp1: Metformin + ADA diet Varied, prespecified target dose Start: 500 mg/day, Max: 2000 mg/day D: every 1 wk increment by 500 mg Grp2: Pioglitazone + PC diet Varied, glucose: FPG > 100 mg, HbA1c: 7% Start: 30 mg, Max: 45 mg D: 8 wks	Grp1 F-B: -0.24 (0.14) Grp2 F-B: -0.42 (0.17) Grp1-Grp2: 0.18 (SE: 0.23)	Grp1 F-B: -3.21 (0.7) Grp2 F-B: -2.59 (1.25) Grp1-Grp2: -0.62		
Gupta, 2013[76]	Grp1: Sitagliptin Titrated (Max: 200mg/day) Grp2: Glimepiride Titrated (Max: 4mg/day) ITT: NR Followup (wks): 24	Grp1: B: 8.03 (0.11) F: 7.26 (0.23) p<0.001 Grp2: B: 8.02 (0.11) F: 7.13 (0.24) p<0.001			
Haak, 2012[77]	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg)	Grp1: B: 8 (0.1) F-B: -0.6 (0.1) Grp2: B: 7.4 (0.1)	Grp1: B: 79.9 (18.4) F-B: -0.7 (0.3) Grp2: B: 76.7 (16)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	ITT: No Followup (wks): 24	F-B: -1.2 (0.1) Between-group difference: Grp2: -0.6 0.1 (-0.8-0.4) p <0.0001	F-B: -0.8 (0.3) Between-group difference: Grp2: -0.2 (-0.9-0.5) p 0.52		
Haak, 2012[77]	Grp1: Metformin Fixed (1000 mg) Grp2: Linagliptin Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 8 (0.1) F-B: -0.6 (0.1) Grp2: B: 8.2 (0.1) F-B: -0.5 (0.1)	Grp1: B: 79.9 (18.4) F-B: -0.7 (0.3) Grp2: B: 79.1 (17.3) F-B: 0.2 (0.3)		
Haak, 2012[77]	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 8 (0.1) F-B: -0.6 (0.1) Grp2: B: 7.1 (0.1) F-B: -1.6 (0.1) Between-group difference: Grp2: -0.5 0.1 (-0.7-0.3) p <0.0001	Grp1: B: 79.9 (18.4) F-B: -0.7 (0.3) Grp2: B: 80.8 (19) F-B: -0.1 (0.3) Between-group difference: Grp2: 0.6 (-0.1-1.3) p 0.1		
Haak, 2012[77]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 7.6 (0.1) F-B: -1.1 (0.1) Grp2: B: 7.1 (0.1) F-B: -1.6 (0.1) Between-group difference: Grp2: -0.5 0.1 (-0.7-0.3) p <0.0001	Grp1: B: 80 (18.5) F-B: -0.5 (0.3) Grp2: B: 76.7 (16) F-B: -0.8 (0.3) Between-group difference: Grp2: -0.2 (-0.9-0.5) p 0.52		
Haak, 2012[77]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Linagliptin Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 7.6 (0.1) F-B: -1.1 (0.1) Grp2: B: 8.2 (0.1) F-B: -0.5 (0.1)	Grp1: B: 80 (18.5) F-B: -0.5 (0.3) Grp2: B: 80.8 (19) F-B: -0.1 (0.3) Grp2: 0.6 (-0.1-1.3) p 0.1		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Haak, 2012[77]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 7.6 (0.1) F-B: -1.1 (0.1) Grp2: B: 7.4 (0.1) F-B: -1.2 (0.1) Between-group difference: Grp2: -0.6 0.1 (-0.8-0.4) p <0.0001	Grp1: B: 80 (18.5) F-B: -0.5 (0.3) Grp2: B: 79.1 (17.3) F-B: 0.2 (0.3)		
Haak, 2012[77]	Grp1: Linagliptin Fixed (5 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 8.2 (0.1) F-B: -0.5 (0.1) Grp2: B: 7.1 (0.1) F-B: -1.6 (0.1) Between-group difference: Grp2: -0.5 0.1 (-0.7-0.3) p <0.0001	Grp1: B: 79.1 (17.3) F-B: 0.2 (0.3) Grp2: B: 76.7 (16) F-B: -0.8 (0.3) Between-group difference: Grp2: -0.2 (-0.9-0.5) p 0.52		
Haak, 2012[77]	Grp1: Linagliptin Fixed (5 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 8.2 (0.1) F-B: -0.5 (0.1) Grp2: B: 7.4 (0.1) F-B: -1.2 (0.1) Between-group difference: Grp2: -0.6 0.1 (-0.8-0.4) p <0.0001	Grp1: B: 79.1 (17.3) F-B: 0.2 (0.3) Grp2: B: 80.8 (19) F-B: -0.1 (0.3) Between-group difference: Grp2: 0.6 (-0.1-1.3) p 0.1		
Haak, 2013[78]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: No Followup (wks): 78	Grp1: B: 8.47 (0.85) F-B: -1.25 (0.1) Grp2: B: 8.61 (0.87) F-B: -1.32 (0.1)			
Haak, 2013[78]	Grp1: Metformin Titrated (Max: 2000 mg)	Grp1: B: 8.47 (0.85)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 78	F-B: -1.25 (0.1) Grp2: B: 8.61 (0.96) F-B: -1.63 (0.1)			
Haak, 2013[78]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: No Followup (wks): 52	Grp1: B: 7.76 (1.1) F-B: -0.42 (0.76) Grp2: B: 7.95 (1.04) F-B: -0.63 (0.83)	Grp1: F-B: -0.4 (2.7) Grp2: F-B: -0.7 (3.2)		
Haak, 2013[78]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 52	Grp1: B: 7.76 (1.1) F-B: -0.42 (0.76) Grp2: B: 8.15 (1.15) F-B: -0.96 (1.05)	Grp1: F-B: -0.4 (2.7) Grp2: F-B: 0.2 (3)		
Hallsten, 2002[79]	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg bid Grp2: Rosiglitazone Varied Start: 2 mg bid, Max: 4 mg bid	Grp1 B: 6.9 (0.2) F: 6.2 (0.2) F-B: -0.7 p: <0.0001 Grp2 B: 6.8 (0.2) F: 6.5 (0.2) F-B: -0.3 p: <0.05 Grp1-Grp2: -0.4 p: NS	Grp1 B: 83.7 (7.9) F: 84.3 (3.5) F-B: 0.6 p: NS Grp2 B: 88.8 (10.8) F: 86.8 F-B: -2 p: <0.05 Grp1-Grp2: -2.6		
Hamann, 2008[80]	Grp1: Metformin + rosiglitazone Varied, glucose: 6.1 mmol/l Max: 2 g; Unclear D: 12 wks Grp2: Metformin + sulfonylurea Varied, glucose: 6.1 mmol/l Max: 2 g; Unclear D: 12 wks	Grp1 F-B: -0.78 (SE: 0.06) Grp2 F-B: -0.86 (SE: 0.06) Grp1-Grp2: 0.09 (CI: -0.08, 0.25)	Grp1 F-B: 2.7 (SE: 0.3) Grp2 F-B: 1.6 (SE: 0.3) Grp1-Grp2: 1.1 p: 0.0016		
Hanefeld, 2004[81]	Grp1: Metformin + sulfonylurea Varied; NR Start: 850 mg, Max: 850 mg tid; NR	Grp1 B: 8.8 (0.97) F: 7.45 (0.06)	Grp1 B: 85.3 (15.1) F: 88.1		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Pioglitazone + sulfonylurea Varied; NR Start: 15 mg, Max: 45 mg; NR	F-B: -1.36 Grp2 B: 8.82 (0.98) F: 7.61 (0.06) F-B: -1.2 Grp1-Grp2: -0.16 p: 0.065	F-B: 2.8 Grp2 B: 84.9 (14.5) F: 83.9 F-B: -1 Grp1-Grp2: 3.8		
Hanefeld, 2007[82]	Grp1: Rosiglitazone Fixed Mean: 4 mg Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1 F-B: -0.3 p: 0.0003 Grp2 F-B: -0.7 p: <0.0001 Grp1-Grp2: 0.4	Grp1 F-B: 1.75 Grp2 F-B: 1.9 Grp1-Grp2: -0.15		
Hanefeld, 2007[82]	Grp1: Rosiglitazone Fixed Mean: 8 mg Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1 F-B: -0.5 p: <0.0001 Grp2 F-B: -0.7 p: <0.0001 Grp1-Grp2: 0.2 (SE: 0.24)	Grp1 F-B: 2.95 Grp2 F-B: 1.9 Grp1-Grp2: 1.05 p: 0.01		
Haring, 2014[83]	Grp1: Metformin + placebo Not specified Grp2: Metformin + empagliflozin Not specified Fixed (25mg) ITT: Yes Followup (wks): 24	Grp1: B: 7.9 (0.88) F: 7.77 (0.07) F-B: -0.13 (0.05) Grp2: B: 7.86 (0.87) F: 7.11 (0.06) F-B: -0.77 (0.05) Between-group difference: Grp2: -0.64 0.07 (-0.77-0.5) p <0.001	Grp1: B: 79.7 (18.6) F: 79.33 (1.28) F-B: -0.45 (0.17) Grp2: B: 81.6 (18.5) F: 79.51 (1.22) F-B: -2.08 (0.17) Between-group difference: Grp2: -1.63 0.24 (-2.11--1.15) p <0.001	Grp1: B: 128.6 (14.7) F: 128.5 (1) F-B: -0.4 (0.7) Grp2: B: 129.6 (14.1) F: 125 (0.9) F-B: -4.5 (0.7) Between-group difference: Grp2: -4.1 1 (-6.2-2.1) p <0.001	
Haring, 2014[83]	Grp1: Metformin + placebo Not specified Grp2: Metformin + empagliflozin Not specified Fixed (10mg) ITT: Yes	Grp1: B: 7.9 (0.88) F: 7.77 (0.07) F-B: -0.13 (0.05) Grp2: B: 7.94 (0.79)	Grp1: B: 79.7 (18.6) F: 79.33 (1.28) F-B: -0.45 (0.17) Grp2: B: 82.2 (19.3)	Grp1: B: 128.6 (14.7) F: 128.5 (1) F-B: -0.4 (0.7) Grp2: B: 130 (15.1)	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Followup (wks): 24	F: 7.22 (0.05) F-B: -0.7 (0.05) Between-group difference: Grp2: -0.57 0.07 (-0.7--0.43) p <0.001	F: 79.71 (1.27) F-B: -2.46 (0.17) Between-group difference: Grp2: -2.01 0.24 (-2.49--1.53) p <0.001	F: 124.6 (1) F-B: -5.2 (0.7) Between-group difference: Grp2: -4.8 1 (-6.9-2.7) p <0.001	
Henry, 2012[84]	Grp1: Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT: No Followup (wks): 24	Grp1: B: 9.14 (1.32) F: 7.79 (1.53) F-B: -1.35 (-1.53-1.18) Grp2: B: 9.21 (1.31) F: 7.13 (1.2) F-B: -2.05 (-2.23-1.88) Between-group difference: Grp1: 0.7 (0.45-0.94) p <0.0001	Grp1: B: 85.75 (19.93) F: 84.45 (19.67) F-B: -1.29 (-1.76--0.82) Grp2: B: 84.24 (19.51) F: 81.62 (18.88) F-B: -2.66 (-3.14--2.19) Between-group difference: Grp1: 1.37 (0.71-2.04) p <0.0001	Grp1: B: 127.9 (14.1) F-B: -1.8 (0.9) Grp2: B: 126.2 (13.9) F-B: -2.9 (0.9)	
Henry, 2012[84]	Grp1: Metformin + placebo Titrated (Mean: 1843.6 mg Median: 2000 mgMax: 2000mg) Grp2: Dapagliflozin + placebo Fixed (5mg) ITT: No Followup (wks): 24	Grp1: B: 9.14 (1.32) F: 7.79 (1.53) p F-B: -1.35 (-1.53-1.18) Grp2: B: 9.14 (1.37) F: 7.96 (1.44) p F-B: -1.19 (-1.36-1.02) Between-group difference: Grp1: 0.7 (0.45-0.94) p <0.0001 Grp2: 0.86 (0.62-1.11) p <0.0001	Grp1: B: 85.75 (19.93) F: 84.45 (19.67) p F-B: -1.29 (-1.76--0.82) Grp2: B: 86.2 (21.13) F: 83.57 (20.85) F-B: -2.61 (-3.07--2.15) Between-group difference: Grp1: 1.37 (0.71-2.04) p <0.0001 Grp2: 0.05 (-0.61-0.72) p 0.8769	Grp1: B: 127.9 (14.1) F-B: -1.8 (0.9) Grp2: B: 128 (14.4) F-B: -4.2 (0.9)	
Henry, 2012[84]	Grp1: Dapagliflozin + placebo Fixed (5mg) Grp2: Metformin + dapagliflozin	Grp1: B: 9.14 (1.37) F: 7.96 (1.44)	Grp1: B: 86.2 (21.13) F: 83.57 (20.85)	Grp1: B: 128 (14.4) F-B: -4.2 (0.9)	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT: No Followup (wks): 24	F-B: -1.19 (-1.36-1.02) Grp2: B: 9.21 (1.31) F: 7.13 (1.2) F-B: -2.05 (-2.23-1.88) Between-group difference: Grp1: 0.86 (0.62-1.11) p <0.0001	F-B: -2.61 (-3.07--2.15) Grp2: B: 84.24 (19.51) F: 81.62 (18.88) F-B: -2.66 (-3.14--2.19) Between-group difference: Grp1: 0.05 (-0.61-0.72) p 0.8769	Grp2: B: 126.2 (13.9) F-B: -2.9 (0.9)	
Henry, 2012[84]	Grp1: Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2: Dapagliflozin + placebo Fixed (10 mg) ITT: No Followup (wks): 24	Grp1: B: 9.03 (1.3) F: 7.6 (1.42) F-B: -1.44 (-1.59-1.29) Grp2: B: 9.03 (1.27) F: 7.59 (1.23) F-B: -1.45 (-1.59-1.31) p Between-group difference: Grp1: 0.01 (-0.2-0.22) p 0.9144 Grp2: 0.53 (0.32-0.74) p <0.0001	Grp1: B: 87.24 (19.42) F: 85.92 (19.1) F-B: -1.36 (-1.83--0.89) Grp2: B: 88.56 (19.72) F: 85.21 (18.86) F-B: -3.33 (-3.8--2.86) Between-group difference: Grp2: -1.97 (-2.64--1.3) p <0.0001	Grp1: B: 130.6 (15.2) F-B: -1.2 (1) Grp2: B: 127.6 (15.6) F-B: -3.3 (0.9)	
Henry, 2012[84]	Grp1: Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 24	Grp1: B: 9.03 (1.3) F: 7.6 (1.42) F-B: -1.44 (-1.59-1.29) Grp2: B: 9.1 (1.28) F: 7.1 (1) F-B: -1.98 (-2.13-1.83) Between-group	Grp1: B: 87.24 (19.42) F: 85.92 (19.1) F-B: -1.36 (-1.83--0.89) Grp2: B: 88.53 (19.33) F: 85.78 (18.67) F-B: -2.73 (-3.19--2.27) Between-group difference: Grp2: -1.37 (-2.03--	Grp1: B: 130.6 (15.2) F-B: -1.2 (1) Grp2: B: 127.8 (13.7) F-B: -4 (0.9	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		difference: Grp1: 0.01 (-0.2-0.22) p 0.9144 Grp2: -0.54 (-0.75-0.33) p <0.0001	0.71) p <0.0001		
Henry, 2012[84]	Grp1: Dapagliflozin + placebo Fixed (10 mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 24	Grp1: B: 9.03 (1.27) F: 7.59 (1.23) p F-B: -1.45 (-1.59-1.31) p Grp2: B: 9.1 (1.28) F: 7.1 (1) p F-B: -1.98 (-2.13-1.83) p Between-group difference: Grp1: 0.53 (0.32-0.74) p <0.0001 Grp2: -0.54 (-0.75-0.33) p <0.0001	Grp1: B: 88.53 (19.33) F: 85.78 (18.67) F-B: -2.73 (-3.19--2.27) Grp2: B: 88.56 (19.72) F: 85.21 (18.86) F-B: -3.33 (-3.8--2.86) Between-group difference: Grp1: -1.37 (-2.03--0.71) p <0.0001 Grp2: -1.97 (-2.64--1.3) p <0.0001	Grp1: B: 127.8 (13.7) F-B: -4 (0.9) Grp2: B: 127.6 (15.6) F-B: -3.3 (0.9)	
Hermann, 1991[85]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Fixed; Varied Start: 3000 mg; Start: 3.5 mg, Max: 14 mg	Grp1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 Grp2 B: 7.7 (1.1) F: 5.4 (0.9) F-B: -2.3 p: <0.001 Grp1-Grp2: 1.4	Grp1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NS Grp2 B: 87.3 (15.6) F: 87.3 (15.9) F-B: 0 p: NS Grp1-Grp2: -0.4		
Hermann, 1991[85]	Grp1: Metformin + diet Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Varied Start: 1000 mg, Max: 3000 mg; Start: 10.5 mg, Max: 14 mg	Grp1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 Grp2 B: 7.8 (1.4) F: 5.7 (0.8) F-B: -2.2 p: <0.001 Grp1-Grp2: 1.3	Grp1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NS Grp2 B: 74.4 (11.4) F: 76 (11.8) F-B: 1.6 p: <0.001 Grp1-Grp2: -2		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Hermann, 1991[85]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glibenclamide Varied Start: 3.5 mg, Max: 10.5 mg	Grp1 B: 6.7 (1.3) F: 5.8 (0.7) F-B: -0.9 p: <0.01 Grp2 B: 6.6 (1.3) F: 5.3 (0.5) F-B: -1.3 p: <0.001 Grp1-Grp2: 0.4	Grp1 B: 76.5 (11.5) F: 76.1 (11.1) F-B: -0.4 p: NS Grp2 B: 84.1 (13.2) F: 87.4 (14.8) F-B: 3.3 p: <0.01 Grp1-Grp2: 3.7		
Hermann, 1994[86]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glyburide Varied Start: 3.5 mg, Max: 10.5 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 6.7 (SE: 0.3) F: 5.3 (SE: 0.1) F-B: -1.3 (SE: 0.2) p: 0.001 Grp1-Grp2: 0.4	Grp1 B: 78.6 (SE: 2.9) F: 78.8 (SE: 2.9) F-B: -0.8 (SE: 0.5) p: >0.1 Grp2 B: 82.6 (SE: 2.7) F: 86.2 (SE: 3.3) F-B: 2.8 (SE: 0.7) p: 0.001 Grp1-Grp2: -3.6		
Hermann, 1994[86]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 1000 mg, Max: 3000 mg; Start: 10.5 mg, Max: 14.0 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 7.8 (SE: 0.3) F: 5.7 (SE: 0.3) F-B: -2.0 (SE: 0.4) p: 0.001 Grp1-Grp2: 1.1 p: >0.1 across all treatment groups	Grp1 B: 78.6 (SE: 2.9) F: 78.8 (SE: 2.9) F-B: -0.2 (SE: 0.5) p: >0.1 Grp2 B: 80.2 (SE: 2.4) F: 81 (SE: 2.5) F-B: 0.7 (SE: 0.4) p: >0.1 Grp1-Grp2: -0.9		
Hermann, 1994[86]	Grp1: Metformin Varied Start: 1000 mg , Max: 3000 mg Grp2: Metformin + glyburide Fixed; Varied Start: 3000 mg; Start: 3.5 mg, Max: 14.0	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	mg	B: 7.8 (SE: 0.3) F: 5.4 (SE: 0.3) F-B: -2.3 (SE: 0.4) p: 0.001 Grp1-Grp2: 1.4 p: >0.1 across all treatment groups			
Hermann, 1994[86]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 2000 mg, Max: 3000 mg; Start: 7.0 mg, Max: 14.0 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 8.4 (SE: 0.4) F: 6.2 (SE: 0.3) F-B: -2.2 (SE: 0.4) p: 0.001 Grp1-Grp2: 1.3 p: >0.1 across all treatment groups			
Hermann, 1994[86]	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 1500 mg; Start: 1.75 mg, Max: 5.25 mg	Grp1 B: 6.9 (SE: 0.3) F: 5.8 (SE: 0.2) F-B: -0.9 (SE: 0.2) p: 0.001 Grp2 B: 6.8 (SE: 0.1) F: 5.6 (SE: 0.1) F-B: -1.2 (SE: 0.1) p: 0.001 Grp1-Grp2: 0.3 p: >0.1 across all treatment groups			
Hermans, 2012[87]	Grp1: Metformin Titrated (1500mgMean: mean additional dose (on top of 1500 mg) was 904 mgadded 500mg qd or bid depending on clinical determination) Grp2: Metformin + saxagliptin	Grp1: B: 7.8 (0.8) F-B: -0.38 (0.06) Grp2: B: 7.7 (0.9) F-B: -0.47 (0.06)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (1500 mg) Fixed (5 mg) ITT: No Followup (wks): 24	Between-group difference: Grp2: -0.1 (-0.26-0.07) p 0.26			
Home, 2007[88]	Grp1: Metformin + rosiglitazone Varied, HbA1c: <=7% Max: 2550 mg; Start: 4 mg, Max: 8 mg Grp2: Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg; Unclear D: 8 wks; NR	Grp1 F-B: -0.48 (CI: -0.59, -0.36) Grp2 F-B: -0.55 (CI: -0.66, -0.44) Grp1-Grp2: 0.07 (CI: -0.09, 0.23)	Grp1 F-B: 2.3 (CI: 1.7, 2.9) Grp2 F-B: 1.1 (CI: 0.6, 1.6) (cohort1), -0.9 (CI: -1.4, -0.4) (cohort2) Grp1-Grp2 (cohort 1): 1.2 (CI: 0.4, 2) p: 0.003; Grp1-Grp2 (cohort 2): 4.3 (CI: 3.6, 5.1) p: <0.001		
Home, 2007[88]	Grp1: Metformin + rosiglitazone Varied, HbA1c: <=7% Max: 2550 mg; Start: 4 mg, Max: 8 mg Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; Unclear D: 8 wks	Grp1 F-B: -0.48 (CI: -0.59, -0.36) Grp2 F-B: -0.55 (CI: -0.67, -0.44) Grp1-Grp2: 0.06 (CI: -0.09, 0.2)	Grp1 F-B: 2.3 (CI: 1.7, 2.9) Grp2 F-B: 3.4 (CI: 2.9, 4) Grp1-Grp2: -1.1		
Home, 2007[88]	Grp1:Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg; Unclear D: 8 wks Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; Unclear	Grp1 F-B: -0.61 (CI: -0.7, -0.51) Grp2 F-B: -0.55 (CI: -0.67, -0.44) Grp1-Grp2: 0.06 (CI: -0.09, 0.2)	Grp1 F-B: -0.9 (CI: -1.4, -0.4) Grp2 F-B: 3.4 (CI: 2.9, 4) Grp1-Grp2: 4.3 (CI: 3.6, 5.1) p: <0.001		
Home, 2009[89]	Grp1: Metformin + rosiglitazone Varied, HbA1c: <=7.0% Max: 2550 mg; Start: 4 mg, Max: 8 mg D: 8 wks; NR Grp2: Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg; Unclear	Grp1 F-B: -0.28 (SE: 0.03) Grp2 F-B: 0.01 (SE: 0.04) Grp1-Grp2: -0.29 (SE: 0.05) p: <0.0001	Grp1 F-B: 3.8 (SE: 0.24) Grp2 F-B: 0 (SE: 0.2) and -1.5 (SE: 0.2) Grp1-Grp2: 3.8		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	D: 8 wks				
Home, 2009[89]	Grp1: Metformin + rosiglitazone Varied, HbA1c: <=7.0% Max: 2550 mg; Start: 4 mg, Max: 8 mg D: 8 wks; NR Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; NR D: Unclear; NR	Grp1 F-B: -0.28 (SE: 0.03) Grp2 F-B: -0.44 (SE: 0.03) Grp1-Grp2: 0.16 (SE: 0.04) p: <0.0001	Grp1 F-B: 3.8 (SE: 0.24) Grp2 F-B: 4.1 (SE: 0.2) Grp1-Grp2: -0.3		
Home, 2009[89]	Grp1: Metformin + sulfonylurea Varied, HbA1c: <=7.0% Max: 2550 mg Grp2: Rosiglitazone + sulfonylurea Varied, HbA1c: <=7.0% Start: 4 mg, Max: 8 mg; NR D: Unclear; NR	Grp1 F-B: -0.18 (SE: 0.04) Grp2 F-B: -0.44 (SE: 0.03) Grp1-Grp2: 0.26 (SE: 0.05) p: <0.0001	Grp1 F-B: -1.5 (SE: 0.2) Grp2 F-B: 4.1 (SE: 0.2) Grp1-Grp2: -5.6 p: <0.001		
Iliadis, 2007[90]	Grp1: Metformin Varied, glucose: euglycemia Max: 1700 mg Grp2: Rosiglitazone Varied, glucose: euglycemia Max: 8 mg	Grp1 F-B: -1.7 (1.1) p: <0.001 Grp2 F-B: -1 (0.7) p: <0.01 Grp1-Grp2: -0.7 (SE: 0.59)	Grp1 F-B: -2.5 (3.5) p: <0.05 Grp2 F-B: -0.3 (3.3) p: NS Grp1-Grp2: -2.2		
Jadzinsky, 2009[91]	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 Wks Grp2: Saxagliptin Fixed	Grp1 F-B: -2 p: <0.0001 Grp2 F-B: -1.7 Grp1-Grp2: -0.3	Grp1 F-B: -1.6 Grp2 F-B: -1.1 Grp1-Grp2: -0.5		
Jadzinsky, 2009[91]	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 Wks Grp2: Metformin + saxagliptin Varied, prespecified target dose Start: 500 mg, Max: 1000 mg; Start: 5mg D: 1 Wks	Grp1 F-B: -2 p: <0.0001 Grp2 F-B: -2.5 p: <0.0001 Grp1-Grp2: 0.5 p: <0.0001	Grp1 F-B: -1.6 Grp2 F-B: -1.8 Grp1-Grp2: 0.2		
Jadzinsky,	Grp1: Metformin	Grp1	Grp1		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2009[91]	Varied Start: 500 mg, Max: 1000 mg D: 1 Wks Grp2: Metformin + saxagliptin Varied, prespecified target dose Start: 500 mg, Max: 1000 mg; Mean: 10 mg D: 1 Wks	F-B: -2 p: <0.0001 Grp2 F-B: -2.5 p: <0.0001 Grp1-Grp2: 0.8 p: <0.0001	F-B: -1.6 Grp2 F-B: -1.4 Grp1-Grp2: -0.2		
Jain, 2006[92]	Grp1: Pioglitazone Varied, glucose: FPG: 69-141 mg/dL Start: 15 mg, Max: 45 mg, Median: 45 mg D: 16 wks Grp2: Glyburide Varied, glucose: FPG: 69-141 mg/dL Start: 5 mg, Max: 15 mg, Median: 10 mg D: 16 wks	Grp1 B: 9.2 (1.26) F: 7.13 (1.26) F-B: -2.07 Grp2 B: 9.2 (1.20) F: 7.18 (1.20) F-B: -2.02 Grp1-Grp2: -0.05 p: 0.669	Grp1 F-B: 3.66 (6.14) p: <0.001 Grp2 F-B: 1.95 (5.35) Grp1-Grp2: 1.71		
Ji, 2015[93]	Grp1: Metformin Titrated 2000mg Grp2: Metformin + Linagliptin Titrated 1000mg Fixed 5mg	Grp1 B: NR F:-.98 (NR) F-B: NR Grp2 B: -0.01 (NR) F: -0.99 (NR) F-B: NR Grp1-Grp2: NR	Grp1 B: NR F: -1.05 (NR F-B: NR Grp2 B: 0.62 (NR) F: -0.44 (NR) F-B: NR Grp1-Grp2: NR		
Jonker, 2009[94]	Grp1: Metformin + glimepiride Fixed Start: 500 mg BD, Max: 1000 mg BD; NR D: 2 Wks Grp2: Pioglitazone + glimepiride Fixed Start: 15 mg OD, Max: 30 mg OD; NR D: 2 Wks	Grp1 B: 7 (0.1) F: 6.3 (SE: 0.1) p:0.146 F-B: -0.7 Grp2 B: 7.1 (0.2) F: 6.5 (SE: 0.1) F-B: -0.6 Grp1-Grp2: -0.1			
Kadoglou, 2011[95]	Grp1: Metformin Fixed (1700mg daily)	Grp1: B: 7.56 (0.64)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Metformin + rosiglitazone Fixed (500mg daily) Fixed (4mg daily) ITT: No Followup (wks): 24	F: 6.87 (1.13) F-B:p <0.001 Grp2: B: 7.58 (0.6) F: 6.6 (1.1) F-B:p <0.001 Between-group difference: p discrepancy (see below)			
Kadowaki, 2013[96]	Grp1: Metformin + placebo Fixed (maintained previous dosage40% on 500 mg/day; 56% on 750 mg/day; 3% on 1000 mg/day; 1.4% on 1500 mg/day) Grp2: Metformin + sitagliptin Fixed (maintained previous dosage43% on 500 mg/day; 51% on 750 mg/day; 3% on 1000mg/day; 4% on 1500 mg/day) Fixed (50mg qd) ITT: No Followup (wks): 12	Grp1: B: 8.3 (1) F: 8.5 (1.2) F-B: 0.3 (0.1-0.5) Grp2: B: 8.1 (0.9) F: 7.5 (0.9) F-B: -0.4 (-0.6-0.2) Between-group difference: Grp1: -0.7 (-0.9-0.5) p <0.001	Grp1: F-B: -0.29 p 0.048 Grp2: F-B: 0.42 p 0.006		
Kahn, 2006[97]	Grp1: Metformin Varied, glucose: <140 mg Start: 500 mg, Max: 2000 mg Grp2: Rosiglitazone Varied, glucose: <140 mg Start: 4 mg, Max: 8 mg	Grp1: Annualized slope: 0.14 (CI: 0.13, 0.16) Grp2: Annualized slope: 0.07 (CI: 0.06, 0.09) Grp2-Grp1: -0.13 (CI: -0.22, -0.05) p: 0.002	Grp1: Annualized slope: -0.3 (CI: -0.4, - 0.2) Grp2: Annualized slope: 0.7 (CI: 0.6, 0.8) Grp1-Grp2: 6.9 (CI: 6.3, 7.4) p: <0.001		
Kahn, 2006[97]	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 2.5 mg, Max: 15 mg	Grp1: Annualized slope: 0.14 (CI: 0.13, 0.16) Grp2: Annualized slope: 0.24 (CI: 0.23, 0.26)	Grp1: Annualized slope: -0.3 (CI: -0.4, - 0.2) Grp2: Annualized slope: -0.2 (CI: -0.3, 0.0)		
Kahn, 2006[97]	Grp1: Rosiglitazone Varied, glucose: <140 mg/dL	Grp1-Grp2: -0.42 (CI: -0.5, -0.33) p: <0.001	Grp1-Grp2: -2.5 (CI: -3.1, -2) p: <0.001		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 4 mg, Max: 8 mg Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 2.5 mg, Max: 15 mg				
Kaku, 2009[98]	Grp1: Metformin Varied Start: 500 mg, Max: 750 mg D: Unclear Grp2: Metformin + pioglitazone Varied Start: 500 mg, Max: 750 mg; Start: 15 mg, Max: 30 mg D: Unclear; 16 wks	Grp1 F-B: 0.25 (0.92) (CI: 0.06, 0.45) p: 0.012 Grp2 F-B: -0.67 (0.8) (CI: -0.84, -0.49) p: <0.0001 Grp1-Grp2: 0.92 (SE: 0.13)	Grp1 F-B: -0.47 Grp2 F-B: 1.68 Grp1-Grp2: -2.15		
Kaku, 2011[99]	Grp1: Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide Titrated (Max: 0.9 mg/d) ITT: No Followup (wks): 52	Grp1: B: 9.18 (0.97) F: 8.2 (0.1) F-B:p Grp2: B: 9.32 (1.08) F: 7.7 (0.1) F-B:p Between-group difference: Grp2: -0.49 (-0.71-0.27) p			
Kaku, 2011[99]	Grp1: Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide Titrated (Max: 0.9 mg/d) ITT: No Followup (wks): 52		Grp1: B: 65.4 (12.9) F-B: 1 Grp2: B: 66.2 (12.6) F-B: -0.8 Between-group difference: Grp2: -1.7 (-2.3--1.2) p		
Kato, 2009[100]	Grp1: Metformin Fixed Max: 500 mg Grp2: Pioglitazone Fixed	Grp1 B: 7.14 (1.4) F: 6.31 (0.9) p:<0.01 F-B: -0.83 Grp2			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Max: 15 mg	B: 7.37 (1.8) F: 6.32 (1.2) p:<0.01 F-B: -1.05 Grp1-Grp2: 0.22			
Kim, 2007[102]	Grp1: Metformin + glimepiride Fixed; Varied, glucose: 7.2 - 9.4 mmol/L Max: 1000 mg; Start: 2 mg, Max: 7 mg Grp2: Rosiglitazone + glimepiride Fixed; Varied, glucose: 7.2 - 9.4 mmol/L Max: 4 mg; Start: 2 mg, Max: 7 mg	Grp1 F-B: -1.1 (CI: -1.4, -0.8) p: <0.001 Grp2 F-B: -1.1 (CI: -1.5, -0.8) p: <0.001 Grp1-Grp2: 0 (SE: 0.24) p: 0.615	Grp1 F-B: -0.5 (CI: -1.2, -0.2) p: 0.187 Grp2 F-B: 1.3 (CI: 0.8, 1.9) p: <0.00 Grp1-Grp2: -1.8 p: <0.001		
Kim, 2014[103]	Grp1: Metformin Titrated (Max: 2500 mg/day) Grp2: Metformin + glimepiride Titrated (Max: 2000 mg/day) Fixed (1-8 mg/day) ITT: NR Followup (wks): 26	Grp1: B: 7.8 (0.7) F: 7 (0.7) p F-B: -0.8 (-0.9-0.6) Grp2: B: 7.9 (0.8) F: 6.6 (0.7) p F-B: -1.2 (-1.3-1.1) p <0.0001 Between-group difference: Grp2: -0.4 (-0.6-0.3) p <0.001			
Kiyici, 2009[104]	Grp1: Metformin Fixed Mean: 850 mg Grp2: Rosiglitazone Fixed Mean: 4 mg	Grp1 B: 6.7 (0.9) F: 6.4 (0.6) p:> 0.05 F-B: -0.3 Grp2 B: 7.1 (0.9) F: 6.4 (0.6) p:0.008 F-B: -0.7 Grp1-Grp2: 0.4			
Kvapil, 2006[105]	Grp1: Metformin + aspart 70/30 Fixed; Varied, glucose: 5 - 8 mmol/L Mean: 1660 mg; Start: 0.2 U/kg, Mean: 0.30 U/kg Start freq: BID, Final freq: BID	Grp1 F-B: -1.7 Grp2 F-B: -1.7 Grp1-Grp2: 0.2 (SE:	Grp1 F-B: 0.8 Grp2 F-B: 0.1 Grp1-Grp2: -0.66 (0.41)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	D: NA; Unclear Grp2: Metformin + glibenclamide Fixed; Varied Mean: 1660 mg; Start: 1.75 mg, Max: 10.5 mg, Mean: 6.58 mg D: NA; Unclear	0.15) p: >0.05	p: 0.1		
Lavalle-Gonzalez, 2013[106]	Grp1: Metformin + placebo Fixed (>=(2,000 mg/day [or >=1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: No Followup (wks): 52	Grp2: B: 7.9 (0.9) F-B: -0.73 (0.05)	Grp2: B: 85.4 (20.7) F-B: -3.7 (0.2) Between-group difference: Grp2: -2.9 (-3.4--2.3) p <0.001	Grp1: B: 128 (13.5) F-B: -1.8 (0.6) Grp2: B: 128.7 (13) F-B: -5.1 (0.6) Between-group difference: Grp1: -3.3 (-5.3-1.4) p no statistical comparison, not prespecified Grp2: -6.6 (-8.5-4.7) p <0.001	
Lavalle-Gonzalez, 2013[106]	Grp1: Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: No Followup (wks): 52	Grp2: B: 7.9 (0.9) F-B: -0.73 (0.05) Between-group difference: Grp2: 0 (-0.12-0.12) p	Grp2: B: 88.7 (22.3) F-B: -3.3 (0.2) Between-group difference: Grp2: -2.4 (-3--1.8) p <0.001	Grp2: B: 128 (13.5) F-B: -0.7 (0.6)	
Lavalle-Gonzalez, 2013[106]	Grp1: Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose]))	Grp1: F-B:p Grp2: B: 8 (0.9) F-B: -0.88 (0.05) p Between-group difference: Grp2: -0.15 (-0.27-	Grp1: F-B:p Grp2: B: 87.6 (20.9) F-B: -1.2 (0.2)	Grp1: F-B:p Grp2: B: 128 (12.7) F-B: -3.5 (0.6) Between-group difference: Grp2: 2.9 (-4.5-1.3) p	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (300mg) ITT: No Followup (wks): 52	0.03) p		<0.001	
Lavalle-Gonzalez, 2013[106]	Grp1: Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: No Followup (wks): 52	Grp1: B: 7.9 (0.9) F-B: -0.73 (0.05) Grp2: B: 8 (0.9) F-B: -0.88 (0.05) Between-group difference: Grp2: -0.15 (-0.27-0.03) p	Grp1: B: 87.6 (20.9) F-B: -1.2 (0.2) Grp2: B: 85.4 (20.7) F-B: -3.7 (0.2) Between-group difference: Grp2: -2.9 (-3.4--2.3) p <0.001	Grp1: F-B: Grp2: B: 128.7 (13) F-B: -4.7 (0.6) Between-group difference: Grp2: -4 (-5.6-2.4) p <0.001	
Lavalle-Gonzalez, 2013[106]	Grp1: Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: No Followup (wks): 52	Grp1: B: 7.9 (0.9) F-B: -0.73 (0.05) Grp2: B: 7.9 (0.9) F-B: -0.73 (0.05) Between-group difference: Grp2: 0 (-0.12-0.12)	Grp1: B: 87.6 (20.9) F-B: -1.2 (0.2) Grp2: B: 88.7 (22.3) F-B: -3.3 (0.2) Between-group difference: Grp2: -2.4 (-3--1.8) p <0.001	Grp1: B: 128 (13.5) F-B: -0.7 (0.6) Grp2: B: 128 (12.7) F-B: -3.5 (0.6) Between-group difference: Grp2: 2.9 (-4.5-1.3) p <0.001	
Lavalle-Gonzalez, 2013[106]	Grp1: Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: No Followup (wks): 26	Grp1: B: 8 (0.9) F-B: -0.17 (0.06) Grp2: B: 7.9 (0.9) F-B: -0.82 (0.04) Between-group difference: Grp2: -0.66 (-0.8-0.52) p Statistical comparison vs PBO not performed (not	Grp1: B: 86.7 (22.5) F-B: -1.1 (0.2) Grp2: B: 87.6 (20.9) F-B: -1.1 (0.2) Between-group difference: Grp2: 0 (-0.6-0.6) p No statistical comparison made, not pre-specified	Grp1: B: 128 (12.7) F-B: 1.5 (0.8) Grp2: B: 128.7 (13) F-B: -5.1 (0.6) Between-group difference: Grp2: -6.6 (-8.5-4.7) p <0.001	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		pre-specified).			
Lavalle-Gonzalez, 2013[106]	Grp1: Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: No Followup (wks): 26	Grp1: B: 8 (0.9) F-B: -0.17 (0.06) Grp2: B: 7.9 (0.9) F-B: -0.79 (0.04) Between-group difference: Grp2: -0.62 (-0.76--0.48) p <0.001	Grp1: B: 86.7 (22.5) F-B: -1.1 (0.2) Grp2: B: 88.7 (22.3) F-B: -3.3 (0.2) Between-group difference: Grp2: -2.5 (-3.1--1.9) p <0.001	Grp1: B: 128 (12.7) F-B: 1.5 (0.8) Grp2: B: 128 (12.7) F-B: -3.8 (0.6) Between-group difference: Grp2: -5.4 (-7.3-3.4) p <0.001	
Lavalle-Gonzalez, 2013[106]	Grp1: Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose]) Grp2: Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: No Followup (wks): 26	Grp1: B: 8 (0.9) F-B: -0.17 (0.06) Grp2: B: 8 (0.9) F-B: -0.94 (0.04) Between-group difference: Grp2: -0.77 (-0.91-0.64) p <0.001	Grp1: B: 86.7 (22.5) F-B: -1.1 (0.2) Grp2: B: 85.4 (20.7) F-B: -3.6 (0.2) Between-group difference: Grp2: -2.9 (-3.5--2.3) p <0.001	Grp1: B: 128 (12.7) F-B: 1.5 (0.8) Grp2: B: 128 (13.5) F-B: -1.8 (0.6) Between-group difference: Grp2: -3.3 (-5.3-1.4) p no statistical comparison, not prespecified	
Lavalle-Gonzalez, 2013[106]	Grp1: Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: No Followup (wks): 26	Grp1: B: 7.9 (0.9) F-B: -0.82 (0.04) Grp2: B: 7.9 (0.9) F-B: -0.79 (0.04) Between-group difference: Grp1: -0.66 (-0.8-0.52) p Statistical comparison vs PBO not performed (not pre-specified). Grp2: -0.62 (-0.76-0.48) p <0.001	Grp1: B: 87.6 (20.9) F-B: -1.1 (0.2) Grp2: B: 88.7 (22.3) F-B: -3.3 (0.2) Between-group difference: Grp1: 0 (-0.6-0.6) p No statistical comparison made, not pre-specified Grp2: -2.5 (-3.1--1.9) p <0.001	Grp1: B: 128 (13.5) F-B: -1.8 (0.6) Grp2: B: 128 (12.7) F-B: -3.8 (0.6) Between-group difference: Grp1: -3.3 (-5.3-1.4) p no statistical comparison, not prespecified Grp2: -5.4 (-7.3-3.4) p <0.001	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Lavalle-Gonzalez, 2013[106]	Grp1: Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: No Followup (wks): 26	Grp1: B: 7.9 (0.9) F-B: -0.82 (0.04) p Grp2: B: 8 (0.9) F-B: -0.94 (0.04) Between-group difference: Grp1: -0.66 (-0.8-0.52) p Statistical comparison vs PBO not performed (not pre-specified). Grp2: -0.77 (-0.91-0.64) p <0.001	Grp1: B: 87.6 (20.9) F-B: -1.1 (0.2) p Grp2: B: 85.4 (20.7) F-B: -3.6 (0.2) Between-group difference: Grp1: 0 (-0.6-0.6) p No statistical comparison made, not pre-specified Grp2: -2.9 (-3.5--2.3) p <0.001	Grp1: B: 128 (13.5) F-B: -0.7 (0.6) p Grp2: B: 128.7 (13) F-B: -4.7 (0.6) Between-group difference: Grp2: -4 (-5.6-2.4) p <0.001	
Lawrence, 2004[107]	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg tid Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1 B: 8.04 (0.9) F: 6.9 (0.5) F-B: -1.12 (0.84) p: <0.01 Grp2 B: 7.43 (0.9) F: 6.62 (0.5) F-B: -0.81 (0.63) p: <0.01 Grp1-Grp2: -0.31 p: NS			
Leiter, 2005[108]	Grp1: Metformin Varied, glucose: <7.0 mmol/L Start: 1500 mg, Max: 2500 mg D: 8 wks Grp2: Metformin + rosiglitazone Fixed; Varied, glucose: < 7 mmol/L Start: 1500 mg, Max: 1500 mg; Start: 4 mg, Max: 8 mg D: 8 wks	Grp1 F-B: -0.14 p: 0.93 Grp2 F-B: p: <0.001 Grp1-Grp2: -0.36 CI: 0.15 - 0.56	Grp1 F-B: no significant weight change Grp2 F-B: 1.6 (CI: 0.9, 2.3)		
List, 2009[109]	Grp1: Metformin Titrated (Max: 1500 mg/d) Grp2: Dapagliflozin	Grp1: B: 7.6 (0.8) F-B: -0.73 (0.1)		Grp1: B: 126 (13) F-B: -0.4 (12.4)	Grp1: B: 68 (10) F-B: 1.1 (9.6)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (5mg) ITT: Yes Followup (wks): 12	Grp2: B: 8 (0.9) F-B: -0.72 (0.09)		Grp2: B: 127 (16) F-B: -6.4 (11.4)	Grp2: B: 70 (10) F-B: -1 (8.9)
List, 2009[109]	Grp1: Metformin Titrated (Max: 1500 mg/d) Grp2: Dapagliflozin Fixed (10 mg) ITT: Yes Followup (wks): 12	Grp1: B: 7.6 (0.8) F-B: -0.73 (0.1) Grp2: B: 8 (0.8) F-B: -0.85 (0.11)		Grp1: B: 126 (13) F-B: -0.4 (12.4) Grp2: B: 126 (13) F-B: -2.9 (12.7)	Grp1: B: 68 (10) F-B: 1.1 (9.6) Grp2: B: 69 (8) F-B: -0.03 (8.9)
Madsbad, 2004[110]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.75 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: -0.75 p: <0.0001 Grp1-Grp2: 0.01	Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: -0.74 p: 0.1544 Grp1-Grp2: 1.68		
Madsbad, 2004[110]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.045 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: 0.25 p: 0.1905 Grp1-Grp2: -0.49	Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: -0.03 p: 0.9602 Grp1-Grp2: 0.97		
Madsbad, 2004[110]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.225 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: -0.34 p: 0.0877 Grp1-Grp2: -0.4	Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: -1.2 p: 0.0184 Grp1-Grp2: 2.14		
Madsbad, 2004[110]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L Start: 1 mg, Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.45 mg	Grp1 F-B: -0.74 p: 0.0001 Grp2 F-B: -0.3 p: 0.1131 Grp1-Grp2: -0.44	Grp1 F-B: 0.94 p: 0.0622 Grp2 F-B: 0.27 p: 0.5838 Grp1-Grp2: 0.67		
Madsbad, 2004[110]	Grp1: Glimepiride Varied, fasting glucose < 7mmol/L	Grp1 F-B: -0.74 p: 0.0001	Grp1 F-B: 0.94 p: 0.0622		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 1 mg, Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.60 mg	Grp2 F-B: -0.7 p: 0.0002 Grp1-Grp2: -0.04	Grp2 F-B: -0.39 p: 0.4391 Grp1-Grp2: 1.33		
Maffioli, 2013[111]	Grp1: Metformin + pioglitazone Fixed (2550 mg) Fixed (30 mg) Grp2: Metformin + glibenclamide Fixed (2550 mg) Fixed (10 mg) ITT: No Followup (wks): 24	Grp1: B: 68.3 (13.6) F: 61.7 (15.8) p F-B:p NS Grp2: B: 66.1 (15.8) F: 57.4 (19.1) p<0.05 F-B:p <0.05 Between-group difference: p <0.05	Grp1: B: 83.5 (9) F: 84.4 (9.2) p F-B:p NS Grp2: B: 83.1 (8.8) F: 83.6 (8.9) pNS F-B:p NS		
Malone, 2003[112]	Grp1: Metformin + lispro 75/25 Varied; Varied, glucose: fasting and premeal glucose<7 mmol/L and 2-h post-prandial glucose <10 mmol/L Max: 2550 mg; Mean: 0.19U/kg in am and 0.14 U/kg in evening D: 4 wks; titrated throughout study period Grp2: Metformin + glibenclamide Varied; Varied, glucose: fasting and pre-meal goal <7mmol/L, 2-hour post-prandial goal <10 mmol/L Max: 2550 mg, Mean: 1968 mg; Mean: 14.2 mg D: 4 wks; titrated throughout study period	Grp2 B: 9.17 (1.5) F: 7.29 (1) F-B: -1.87 (1.35) p: <0.001 Grp1 B: 9.27 (1.55) p: 0.181 F: 7.33 (1.14) p: 0.661 F-B: -1.98 (1.28) p: <0.001 Grp1-Grp2: 011 (SE: 0.33) p: 0.288	Grp1 B: 83 (15.2) F: 84 (15.1) F-B: 1 Grp2 B: 81.7 (15.7) F: 82.2 (15.4) p: 0.33 F-B: 0.5 Grp1-Grp2: 0.5		
Marre, 2002[113]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glibenclamide Varied Start: 5 mg, Max: 20 mg	Grp1 B: 8.09 (1.84) F: 7.89 F-B: -0.2 Grp2 B: 7.88 (1.65) F: 7.58	Grp1 B: 84.9 (17.6) F: 84.1 F-B: -0.8 Grp2 B: 82.5 (15.4) F: 83.4		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		F-B: -0.3 Grp1-Grp2: 0.1 p: NS	F-B: 0.9 Grp1-Grp2: -1.7		
Marre, 2002[113]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Grp1 B: 8.09 (1.84) F: 7.89 F-B: -0.2 Grp2 B: 7.89 (1.62) F: 6.69 F-B: -1.2 Grp1-Grp2: 1 p: <0.05	Grp1 B: 84.9 (17.6) F: 84.1 F-B: -0.8 Grp2 B: 84.7 (15.1) F: 85.3 F-B: 0.6 Grp1-Grp2: -1.4		
Marre, 2002[113]	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 10 mg	Grp1 B: 8.09 (1.84) F: 7.89 F-B: -0.2 Grp2 B: 7.62 (1.61) F: 6.72 F-B: -0.9 Grp1-Grp2: 0.7 p: <0.05	Grp1 B: 84.9 (17.6) F: 84.1 F-B: -0.8 Grp2 B: 83.1 (13.3) F: 84.1 F-B: 1 Grp1-Grp2: -1.8		
Moon, 2014[114]	Grp1: Metformin + glimepiride Fixed (Mean: 1426.5mgdose the same as met dose prior to study, discontinued if FBG was controlled at target level with glimepiride<=0.25mg/day) Titrated (Mean: 4.3Max: 8mgstarting 1mg/day, increased to 2mg/day at second week, up to 8mg/day at week 3,5,7 with target FBG of 90-130mg/dl as per the investigator's discretion) Grp2: Metformin + insulin glargine Fixed (Mean: 1365.1mgdose the same as met dose prior to study) Titrated (Mean: 22.8 unitsstarting at 0.2U/kg of body weight, titrated every 3 days by 2IU with target FBG of 90-130mg/dl as per the investigator's discretion; discontinued if FBG was	Grp1: B: 8.9 (1.3) F: 7.2 (1) F-B: -1.8 (1.2) Grp2: B: 8.8 (1.2) F: 7 (0.7) F-B: -1.8 (1.3) Between-group difference: p 0.43	Grp1: B: 66 (11.1) F-B: 0 (3.1) Grp2: B: 62.7 (9.1) F-B: 1.7 (2.7) Between-group difference: p 0.02		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	controlled at target level with glargine<=8IU) ITT: No Followup (wks): 48				
Nakamura, 2000[115]	Grp1: Pioglitazone Fixed Start: 30 mg Grp2: Glibenclamide Fixed Start: 5 mg	Grp1 B: 7.7 (1.2) F: 6.8 (1.0) F-B: -0.9 p: <0.05 Grp2 B: 7.8 (1.1) F: 6.9 (1.2) F-B: -0.9 p: <0.05 Grp1-Grp2: 0			
Nakamura, 2004[116]	Grp1: Pioglitazone Fixed Start: 30 mg Grp2: Glibenclamide Fixed Start: 5 mg	Grp1 F-B: 1.7 (1) p: <0.05 Grp2 F-B: 1.5 (1.1) p: <0.05 Grp1-Grp2: 0.2 (SE: 0.62)			
Natali, 2004[117]	Grp1: Metformin Fixed Start: 500 mg tid Grp2: Rosiglitazone Fixed Start: 4 mg bid		Grp1 B: 80.4 (SEM 10.1) F: 80.9 F-B: 0.5 (0.5) p: NS Grp2 B: 77.3 (SEM 12.5) F: 76.7 F-B: -0.6 (0.4) p: NS Grp1-Grp2: 1.1 p: NS		
Nauck, 2007[118]	Grp1: Metformin + glipizide Varied; Varied, glucose: <6.1 mmol/l NR; Start: 5 mg, Max: 20 mg D: Unclear; 18 wks Grp2: Metformin + sitagliptin Varied; Fixed NR	Grp1-Grp2: -0.01 (CI: -0.09, 0.08)	Grp1-Grp2: -2.5 (CI: -3.1, -2) p: <.001		
Nauck, 2009[119]	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin	Grp1: B: 8 (0.9) F-B: -0.1 (0.1) Grp2:	Between-group difference: Grp2: -0.3 (-0.9-0.4)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT: No Followup (wks): 26	B: 7.9 (0.8) F-B: -0.6 (0.1) Between-group difference: p <0.001			
Nauck, 2009[119]	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT: No Followup (wks): 26	Grp1: B: 8 (0.9) F-B: -0.1 (0.1) Grp2: B: 7.9 (0.7) F-B: -0.6 (0.1) Between-group difference: p <0.001	Between-group difference: Grp2: 0 (-0.7-0.7)		
Nauck, 2011[120]	Grp1: Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2: Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT: No Followup (wks): 104	Grp1: B: 7.74 (0.9) F-B: -0.14 (-0.25-0.03) Grp2: B: 7.69 (0.9) F-B: -0.32 (-0.42-0.21) p Between-group difference: Grp2: -0.18 (-0.33-0.3) p 0.0211	Grp1: B: 87.6 F-B: 1.4 (0.9-1.8) Grp2: B: 88.4 F-B: -3.7 (-4.2--3.2) Between-group difference: Grp2: -5.1 (-5.7--4.4)	Grp1: B: 133.8 F-B: 1.2 (-0.4-2.8) Grp2: B: 132.8 F-B: -2.7 (-4.2-1.2) Between-group difference: Grp2: -3.9 (-6.1-1.7)	
Nauck, 2014[121]	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT: Yes Followup (wks): 26	Grp1: B: 8.1 (1.1) F: 7.99 F-B: 0.03 (0.07) Grp2: B: 8.1 (1.1) F: 7.37 F-B: -0.61 (0.05) Between-group difference: Grp2: -0.64 p <0.001	Grp1: B: 87 (17) F-B: -1.67 (0.15) Grp2: B: 86 (17) F-B: -1.46 (0.15)	Grp1: B: 127 (13) F-B: -0.5 (0.7) Grp2: B: 129 (14) F-B: -0.8 (0.7) Between-group difference: p >0.05	Grp1: B: 73.7 (10.3) F-B: 0.3 (0.5) p >0.05 Grp2: B: 74.1 (10.9) F-B: -0.1 (0.5) p >0.05
Nauck, 2014[121]	Grp1: Metformin + placebo Fixed (>=1500 mg/day)	Grp1: B: 8.1 (1.1)	Grp1: B: 87 (17)	Grp1: B: 128 (13)	Grp1: F-B: -0.2 (0.7)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Yes Followup (wks): 26	F: 7.99 F-B: 0.03 (0.07) Grp2: B: 8.2 (1.1) F: 6.95 F-B: -1.01 (0.06) Grp2: -1.05 p <0.001	F-B: -1.67 (0.15) Grp2: B: 87 (17) F-B: -3.23 (0.15) Between-group difference: p <0.001	F-B: 1.1 (0.9) Grp2: B: 127 (13) F-B: -1.9 (0.7) Between-group difference: p <0.05	Grp2: F-B: -0.1 (0.5) Between-group difference: p >0.05
Nauck, 2014[121]	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Yes Followup (wks): 26	Grp1: B: 8.1 (1.1) F: 7.99 p F-B: 0.03 (0.07) p Grp2: B: 8.1 (1.1) F: 6.72 p F-B: -1.22 (0.05) p Between-group difference: Grp2: -1.26 p <0.001	Grp1: B: 87 (17) F-B: -1.67 (0.15) Grp2: B: 86 (18) F-B: -2.63 (0.15) Between-group difference: p <0.001	Grp1: B: 128 (13) F-B: 1.1 (0.9) Grp2: B: 128 (14) F-B: -1.4 (0.7) Between-group difference: p <0.05	Grp1: F-B: -0.2 (0.7) p Grp2: F-B: 1.9 (0.5) Between-group difference: p <0.05
Nauck, 2014[121]	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Yes Followup (wks): 26	Grp1: B: 8.1 (1.1) F: 7.37 p F-B: -0.61 (0.05) p Grp2: B: 8.2 (1.1) F: 6.95 p F-B: -1.01 (0.06) p Between-group difference: Grp1: -0.64 p <0.001 Grp2: -1.05 p <0.001	Grp1: B: 86 (17) F-B: -1.46 (0.15) Grp2: B: 86 (18) F-B: -2.63 (0.15) Between-group difference: p <0.001	Grp1: B: 128 (13) F-B: 1.1 (0.9) Grp2: B: 129 (14) F-B: -1.7 (0.7) Between-group difference: p <0.05	Grp1: F-B: -0.2 (0.7) Grp2: F-B: 2.6 (0.5) Between-group difference: p <0.001
Nauck, 2014[121]	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Yes Followup (wks): 26	Grp1: B: 8.1 (1.1) F: 7.37 p F-B: -0.61 (0.05) p Grp2: B: 8.1 (1.1) F: 6.72 p F-B: -1.22 (0.05) p Between-group	Grp1: B: 86 (17) F-B: -1.46 (0.15) Grp2: B: 87 (17) F-B: -3.23 (0.15) Between-group difference: p <0.001	Grp1: B: 127 (13) F-B: -1.9 (0.7) p Grp2: B: 129 (14) F-B: -1.7 (0.7) p Between-group difference: p <0.05	Grp1: F-B: -0.1 (0.5) p Grp2: F-B: 1.9 (0.5) p Between-group difference: p >0.05 p <0.05

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		difference: Grp1: -0.64 p <0.001 Grp2: -1.26 p <0.001		p <0.05	
Nauck, 2014[121]	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT: Yes Followup (wks): 52	Grp1: F-B:p Grp2: B: 8.1 (1.1) F: 7.57 F-B: -0.39 (0.06)	Grp1: F-B:p Grp2: B: 86 (17) F-B: -1.53 (0.22)	Grp1: B: 127 (13) F-B: -1.9 (0.7) Grp2: B: 128 (14) F-B: -1.4 (0.7) p Between-group difference: p <0.05 p <0.05	Grp1: F-B: -0.1 (0.5) Grp2: F-B: 2.6 (0.5) Between-group difference: p >0.05 p <0.001
Nauck, 2014[121]	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Yes Followup (wks): 52	Grp1: F-B:p Grp2: B: 8.2 (1.1) F: 7.08 F-B: -0.87 (0.06) Between-group difference: Grp2: -0.47 (-0.63-0.31) p <0.001	Grp1: F-B:p Grp2: B: 87 (17) F-B: -3.03 (0.22) Between-group difference: Grp2: -1.5 p <0.001	Grp1: F-B:p Grp2: B: 129 (14) F-B: -0.8 (0.7) Between-group difference: p >0.05	Grp1: F-B:p Grp2: F-B: -0.3 (0.5)
Nauck, 2014[121]	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Yes Followup (wks): 52	Grp1: F-B:p Grp2: B: 8.1 (1.1) F: 6.83 F-B: -1.1 (0.06) Between-group difference: Grp2: -0.71 (-0.87-0.55) p <0.001	Grp1: F-B:p Grp2: B: 86 (18) F-B: -2.6 (0.23) Between-group difference: Grp2: -1.07 p <0.05	Grp1: F-B:p Grp2: B: 127 (13) F-B: -0.5 (0.7)	Grp1: F-B:p Grp2: F-B: 2.1 (0.5) Between-group difference: p <0.001
Nauck, 2014[121]	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day)	Grp1: B: 8.1 (1.1) F: 7.57 F-B: -0.39 (0.06) Grp2:	Grp1: B: 86 (17) F-B: -1.53 (0.22) Grp2: B: 86 (18)	Grp1: F-B:p Grp2: B: 128 (14) F-B: -0.5 (0.7) p	Grp1: F-B:p Grp2: F-B: 2.4 (0.5) Between-group

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (0.75 mg/week) ITT: Yes Followup (wks): 52	B: 8.2 (1.1) F: 7.08 F-B: -0.87 (0.06) Between-group difference: Grp2: -0.47 (-0.63-0.31) p <0.001	F-B: -2.6 (0.23) Between-group difference: Grp2: -1.07 p <0.05	Between-group difference: p >0.05	difference: p <0.001
Nauck, 2014[121]	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Yes Followup (wks): 52	Grp1: B: 8.1 (1.1) F: 7.57 F-B: -0.39 (0.06) Grp2: B: 8.1 (1.1) F: 6.83 F-B: -1.1 (0.06) Between-group difference: Grp2: -0.71 (-0.87-0.55) p <0.001	Grp1: B: 86 (17) F-B: -1.53 (0.22) Grp2: B: 87 (17) F-B: -3.03 (0.22) Between-group difference: Grp2: -1.5 p <0.001	Grp1: B: 127 (13) F-B: -0.5 (0.7) Grp2: B: 128 (14) F-B: -0.5 (0.7) Between-group difference: p >0.05	Grp1: F-B: -0.3 (0.5) Grp2: F-B: 2.4 (0.5) Between-group difference: p <0.001
Oz Gul, 2010[122]	Grp1: Rosiglitazone Fixed (4 mg/day) Grp2: + placebo ITT: Yes Followup (wks): 12	Grp1: B: 7.3 (1.3) F: 6.2 (0.5) p0.003 F-B:p Grp2: B: 7.3 (0.9) F: 7.2 (0.7)			Grp1: F-B: -0.3 (0.5) Grp2: F-B: 2.1 (0.5) Between-group difference: p <0.001
Oz Gul, 2010[122]	Grp1: Pioglitazone Fixed (30 mg/day) Grp2: + placebo ITT: Yes Followup (wks): 12	Grp1: B: 7.6 (1.5) F: 6.5 (0.6) p<0.001 F-B:p Grp2: B: 7.3 (0.9) F: 7.2 (0.7) F-B:p			
Pavo, 2003[123]	Grp1: Metformin Varied Start: 850 mg, Max: 2550 mg Grp2: Pioglitazone Varied	Grp1 B: 8.6 F: 7.1 F-B: -1.5 p: <0.0001 Grp2	Grp1 B: 86.1 (15.6) F: 86.8 F-B: -0.7 (0.4) Grp2		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start: 30 mg, Max: 45 mg	B: 8.6 F: 7.3 F-B: -1.3 p: <0.0001 Grp1-Grp2: -0.2 p: 0.28	B: 88.9 (15.9) F: 90.2 F-B: 2.4 Grp1-Grp2: -3.1 p: <0.0001		
Perez, 2009[125]	Grp1: Metformin Fixed Start: 850 mg Grp2: Pioglitazone Fixed	Grp1 F-B: -0.99 Grp2 F-B: -0.96 Grp1-Grp2: -0.03 (0.17)	Grp1 F-B: -1.28 Grp2 F-B: 1.64 Grp1-Grp2: -2.92		
Perez, 2009[125]	Grp1: Metformin Fixed Start: 850 mg Grp2: Metformin + pioglitazone Fixed	Grp1 F-B: -0.99 Grp2 F-B: -1.83 p: <0.0001 Grp1-Grp2: 0.84 (SE: 0.17)	Grp1 F-B: -1.28 Grp2 F-B: 0.69 Grp1-Grp2: -1.97		
Petrica, 2009[126]	Grp1: Metformin + rosiglitazone Fixed (1700 mg/day) Fixed (4 mg/day) Grp2: Metformin + glimepiride Fixed (1700 mg/day) Fixed (4 mg/day) ITT: No Followup (wks): 48	Grp1: B: 7.72 (1.2) F: 6.74 (0.81) p0.39 F-B:p Grp2: B: 7.58 (1.01) F: 7.06 (0.86) F-B:p			
Pfutzner, 2005[127]	Grp1: Pioglitazone Fixed Start: 45 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 6 mg	Grp1 B: 7.52 (0.85) F: 6.71 (0.89) F-B: -0.81 p: <0.05 Grp2 B: 7.44 (0.89) F: 6.83 (0.85) F-B: -0.61 p: <0.05 Grp1-Grp2: -0.2			
Pfutzner, 2011[128]	Grp1: Metformin + pioglitazone Fixed (1700 mg/d) Fixed (30 mg/d) Grp2: Metformin + glimepiride Fixed (1700 mg/d)	Grp1: B: 7.3 (0.9) F: 6.5 (0.9) F-B: -0.8 (0.9) p <0.05	Grp1: B: 96.2 (17.5) F: 96.9 (17.8) F-B:p <0.05 Grp2:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (2mg/d) ITT: No Followup (wks): 24	Grp2: B: 7.3 (0.8) F: 6.3 (0.8) F-B: -1 (0.9) p <00.05 Between-group difference: p NS	B: 94.1 (18) F: 94.8 (18.2) F-B:p <0.05		
Pfutzner, 2011[129]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Saxagliptin + placebo Fixed (10 mg) ITT: No Followup (wks): 76	Grp1: B: 9.43 (0.07) F-B: -1.79 (0.07) (-1.93-1.65) p Grp2: B: 9.61 (0.08) F-B: -1.55 (0.08) (-1.7-1.4)	Grp1: B: 82.8 (17.5) F-B: -1 Grp2: B: 83.1 (16.9) F-B: -0.3		
Pfutzner, 2011[129]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 76	Grp1: B: 9.43 (0.07) F-B: -1.79 (0.07) (-1.93-1.65) Grp2: B: 9.41 (0.07) F-B: -2.31 (0.07) (-2.44-2.18) p Between-group difference: Grp2: -0.52 0.1 (-0.71-0.33) p <0.0001	Grp1: B: 82.8 (17.5) F-B: -1 Grp2: B: 82.1 (16.3) F-B: -1.2		
Pfutzner, 2011[129]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 76	Grp1: B: 9.43 (0.07) F-B: -1.79 (0.07) (-1.93-1.65) p Grp2: B: 9.53 (0.07) F-B: -2.33 (0.07) (-2.46-2.2) p Between-group difference: Grp2: -0.54 0.1 (-0.73-	Grp1: B: 82.8 (17.5) F-B: -1 Grp2: B: 82.5 (16.9) F-B: -0.7		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		0.35) p <0.0001			
Pfutzner, 2011[129]	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 76	Grp1: B: 9.61 (0.08) F-B: -1.55 (0.08) (-1.7-1.4) p Grp2: B: 9.41 (0.07) F-B: -2.31 (0.07) (-2.44-2.18) p Between-group difference: Grp2: -0.52 0.1 (-0.71-0.33) p <0.0001	Grp1: B: 83.1 (16.9) F-B: -0.3 Grp2: B: 82.5 (16.9) F-B: -0.7		
Pfutzner, 2011[129]	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 76	Grp1: B: 9.61 (0.08) F-B: -1.55 (0.08) (-1.7-1.4) p Grp2: B: 9.53 (0.07) F-B: -2.33 (0.07) (-2.46-2.2) p Between-group difference: Grp2: -0.54 0.1 (-0.73-0.35) p <0.0001	Grp1: B: 83.1 (16.9) F-B: -0.3 Grp2: B: 82.1 (16.3) F-B: -1.2		
Pratley, 2010[130]	Grp1: Metformin + sitagliptin Varied NR; Max: 100 mg D: NR Grp2: Metformin + liraglutide Varied, HbA1c: 7.5-10% NR; Start: 0.6 mg, Max: 1.2 mg D: NR	Grp1 F-B: -0.9 (CI: -1.03, -0.77) Grp2 F-B: -1.24 (CI: -1.37, -1.11) Grp1-Grp2: 0.34 (CI: 0.16, 0.51) p<0.0001	Grp1 F-B: -0.96 (CI: -1.5, -0.42) Grp2 F-B: -3.38 (CI: -3.91, -2.84) Grp1-Grp2: 2.42 (CI: 1.7, 3.14)		
Pratley, 2010[130]	Grp1: Metformin + sitagliptin Varied NR; Max: 100 mg D: NR Grp2: Metformin + liraglutide Varied, HbA1c: 7.5-10%	Grp1 F-B: -0.9 (CI: -1.03, -0.77) Grp2 F-B: -1.5 (CI: -1.63, -1.37)	Grp1 F-B: -0.96 (CI: -1.5, -0.42) Grp2 F-B: -2.86 (CI: -3.39, -2.32)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Unclear; Start: 0.6 mg, Max: 1.8 mg D: NR	Grp1-Grp2: 0.6 (CI: 0.43, 0.77) p<0.0001	Grp1-Grp2: 1.9 (CI: 1.18, 2.61)		
Pratley, 2014[131]	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 26	Grp1: B: 8.5 F-B: -0.65 (0.094) Grp2: B: 8.5 F-B: -1.22 (0.094)	Grp1: B: 81.69 F-B: -0.8 (0.283) Grp2: B: 82.69 F-B: -0.57 (0.28)		
Pratley, 2014[131]	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 26	Grp1: B: 8.5 F-B: -0.65 (0.094) Grp2: B: 8.43 F-B: -1.55 (0.09)	Grp1: B: 81.69 F-B: -0.8 (0.283) Grp2: B: 81.82 F-B: 0.13 (0.29)		
Pratley, 2014[131]	Grp1: Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 26	Grp1: B: 8.5 F-B: -0.65 (0.094) Grp2: B: 8.3 F-B: -0.52 (0.1)	Grp1: B: 81.69 F-B: -0.8 (0.283) Grp2: B: 86.57 F-B: -1.17 (0.268)		
Pratley, 2014[131]	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 26	Grp1: B: 8.39 F-B: -1.11 (0.092) Grp2: B: 8.43 F-B: -1.55 (0.09)	Grp1: B: 81.79 F-B: -1.25 (0.27) Grp2: B: 86.57 F-B: -1.17 (0.268)		
Pratley, 2014[131]	Grp1: Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 26	Grp1: B: 8.39 F-B: -1.11 (0.092) Grp2: B: 8.3 F-B: -0.52 (0.1)	Grp1: B: 81.79 F-B: -1.25 (0.27) Grp2: B: 81.82 F-B: 0.13 (0.29)		
Pratley, 2014[131]	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg)	Grp1: B: 8.39 F-B: -1.11 (0.092) Grp2:	Grp1: B: 81.79 F-B: -1.25 (0.27) Grp2:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (25 mg) ITT: Yes Followup (wks): 26	B: 8.5 F-B: -1.22 (0.094)	B: 82.69 F-B: -0.57 (0.28)		
Pratley, 2014[131]	Grp1: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 26	Grp1: B: 8.5 F-B: -1.22 (0.094) Grp2: B: 8.3 F-B: -0.52 (0.1)	Grp1: B: 82.69 F-B: -0.57 (0.28) Grp2: B: 81.82 F-B: 0.13 (0.29)		
Pratley, 2014[131]	Grp1: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 26	Grp1: B: 8.43 F-B: -1.55 (0.09) Grp2: B: 8.3 F-B: -0.52 (0.1	Grp1: B: 86.57 F-B: -1.17 (0.268) Grp2: B: 81.82 F-B: 0.13 (0.29)		
Qiu, 2014[132]	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin + canagliflozin Fixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (150mg BID) ITT: Yes Followup (wks): 18	Grp1: B: 7.7 (0.9) F: 7.6 (0.1) F-B: -0.01 (0.07) Grp2: B: 7.6 (0.9) F: 6.9 (0.1) F-B: -0.61 (0.07) Between-group difference: Grp2: -0.6 p <0.001	Grp1: B: 90.5 (18.1) F-B: -0.5 Grp2: B: 90.2 (19.1) F-B: -3.1 Between-group difference: Grp2: -2.6 p <0.001	Grp1: B: 128.6 (11) F-B: 3.3 (1.1) Grp2: B: 128.2 (12) F-B: -2.4 (1.1) Between-group difference: Grp2: -5.7 (-8.7-2.6) p	Grp1: F-B: 0 Grp2: F-B: 1.4
Qiu, 2014[132]	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin + canagliflozin Fixed (Mean: 2137mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks	Grp1: B: 7.7 (0.9) F: 7.6 (0.1) F-B: -0.01 (0.07) Grp2: B: 7.6 (0.9) F: 7.2 (0.1) F-B: -0.45 (0.07) Between-group	Grp1: B: 90.5 (18.1) F-B: -0.5 Grp2: B: 91.2 (23.9) F-B: -2.6 Between-group difference: Grp2: -2.1 p <0.001	Grp1: B: 128.6 (11) F-B: 3.3 (1.1) Grp2: B: 131.1 (12.4) F-B: -2.1 (1.1) Between-group difference: Grp2: -5.4 (-8.4-2.3)	Grp1: F-B: 0 Grp2: F-B: 0.9

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	prior to screening) Fixed (50mg BID) ITT: Yes Followup (wks): 18	difference: Grp2: -0.44 p <0.001			
Ramachandran, 2004[133]	Grp1: Metformin Varied Start: 250 mg, Max: 850 mg Grp2: Pioglitazone Varied Start: 15 mg, Max: 30 mg	Grp1 B: 9.6 (2.4) F: 8.2 (2.5) F-B: -1.4 p: 0.05 Grp2 B: 9.3 (1.8) F: 6.7 (1.3) F-B: -2.6 p: 0.01 Grp1-Grp2: 1.2	Grp1 B: 68.9 (9.1) F: 67.8 (7.9) F-B: -1.1 Grp2 B: 67.7 (11.5) F: 67 (11.4) F-B: -0.7 Grp1-Grp2: -0.4		
Ramachandran, 2004[133]	Grp1: Metformin Varied Start: 250 mg, Max: 850 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg	Grp1 B: 9.6 (2.4) F: 8.2 (2.5) F-B: -1.4 p: <0.05 Grp2 B: 10.2 (2.2) F: 7.7 (1.7) F-B: -2.5 p: <0.01 Grp1-Grp2: 1.1	Grp1 B: 67.7 (11.5) F: 67 (11.4) F-B: -0.7 Grp2 B: 65.7 (9.1) F: 67.5 (9.2) F-B: 1.8 p: <0.05 Grp1-Grp2: -2.5		
Ramachandran, 2004[133]	Grp1: Pioglitazone Varied Start: 15 mg, Max: 30 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg	Grp1 B: 9.3 (1.8) F: 6.7 (1.3) F-B: -2.6 p: <0.01 Grp2 B: 10.2 (2.2) F: 7.7 (1.7) F-B: -2.5 p: <0.01 Grp1-Grp2: -0.1	Grp1 B: 68.9 (9.1) F: 67.8 (7.9) F-B: -1.1 Grp2 B: 65.7 (9.1) F: 67.5 (9.2) F-B: 1.8 p: <0.05 Grp1-Grp2: -2.9		
Raskin, 2007[134]	Grp1: Metformin + glargine Fixed; Varied, glucose: 4.4 - 6.1 mmol/L before breakfast and dinner NR; Start: 12 U/day, Mean: 0.57 IU/kg Start freq: QD, Final freq: QD Grp2: Metformin + aspart 70/30 Fixed; Varied, glucose: 4.4 - 6.1 mmol/L NR; Start: 12 IU/day, Mean: 0.91 IU/kg	Grp1 F-B: -2.46 (SE: 1.6) Grp2 F-B: -2.89 (SE: 1.6) Grp1-Grp2: 0.43 (SE: 2.26) p: 0.035	Grp1 F-B: 3 (4.3) Grp2 F-B: 5.6 (4.6) Grp1-Grp2: -2.6 p: 0.0004		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Start freq: BID, Final freq: BID				
Raz, 2008[188]	Grp1: Metformin Fixed NR Grp2: Metformin + sitagliptin Fixed Max: 2550 mg; Mean: 100 mg	Grp1 F-B: 0 (CI: -0.2, 0.3) Grp2 F-B: -1 (CI: -1.3, -0.7) p: <0.001 Grp1-Grp2: -1 (CI: -1.4, -0.6) p: <0.001	Grp1 F-B: -0.5 Grp2 F-B: -0.5 Grp1-Grp2: 0		
Reasner, 2011[135]	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 44	Grp1: B: 9.8 (1.8) F-B: -1.8 (-1.9-1.6) Grp2: B: 9.9 (1.8) F-B: -2.3 (-2.4-2.1) Between-group difference: Grp2: -0.5 (-0.7-0.3) p <0.001	Grp1: B: 97.6 (25.3) F-B: -1.2 (-1.7--0.6) Grp2: B: 95.4 (22.9) F-B: -1.1 (-1.7--0.6)		
Ridderstrale, 2014[136]	Grp1: Metformin + glimepiride Fixed (Mean: 2.71 mg/day (mean max titrated dose of glimep(>=1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Titrated (Max: 4mg) Grp2: Metformin + empagliflozin Fixed ((ГёÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Fixed (25mg) ITT: No Followup (wks): 104	Grp1: B: 7.92 (0.86) F: 7.37 (7.31-7.43) F-B: -0.55 (-0.61-0.49) Grp2: B: 7.92 (0.81) F: 7.26 (7.31-7.43) p F-B: -0.66 (-0.72-0.6) Between-group difference: Grp2: -0.11 (-0.19-0.02) p <0.0001 (non-inferiority), 0.0153 (superiority)	Grp1: B: 83 (19.2) F: 84.1 (83.9-84.4) F-B: 1.3 (1.1-1.6) Grp2: B: 82.5 (19.2) F: 79.7 (83.9-84.4) F-B: -3.1 (-3.4--2.9) Between-group difference: Grp2: -4.5 (-4.8--4.1) p <0.0001	Grp1: B: 133.5 (16) F: 136 (135.2-136.8) F-B: 2.5 (1.7-3.4) Grp2: B: 133.4 (15.9) F: 130.4 (135.2-136.8) F-B: -3.1 (-3.9-2.2) Between-group difference: Grp2: -5.6 (-6.8-4.4) p <0.0001	
Rigby, 2009[137]	Grp1: Metformin + rosiglitazone Fixed Mean: 4 mg Grp2: Metformin + sitagliptin Fixed Mean: 100 mg	Grp1 B: 8.09 F: 7.53 F-B: -0.6 (CI: -0.83, -0.32) p: <0.0001 Grp2	Grp1 F-B: 0.26 p: 0.5935 Grp2 F-B: -1.15 p: 0.0008 Grp1-Grp2: 1.41		Grp1: F-B: 0.59 (9.8) Grp2: F-B: -1.36 (9.2)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		B: 8.19 F: 7.79 F-B: -0.4 (CI: -0.64, -0.13) p: 0.0087 Grp1-Grp2: -0.2			
Robbins, 2007[138]	Grp1: Metformin + glargine Fixed; Varied, glucose: <6.7 mmol/l Start: 500 mg tid, Max: 1000 mg tid, Mean: 1636 mg; Mean: 0.6 U/kg Start: QD, Final: QD Grp2: Metformin + insulin lispro 50/50 Fixed; Varied, glucose: <6.7 mmol/L Start: 500 mg tid, Max: 1000 mg tid, Mean: 1641 mg; Mean: 0.7 U/kg Start freq: NR, Final freq: tid	Grp1 F-B: -0.4 (0.9) Grp2 F-B: -0.7 (0.9) p: <0.001 Grp1-Grp2: 0.3 (SE: 0.32) p: <0.001	Grp1 B: 88.1 (19) F: 87.6 (19.3) p: 0.04 F-B: -0.5 Grp2 B: 89.1 (20.4) F: 90 (20.5) p: <0.001 F-B: 0.9 Grp1-Grp2: -1.4 p: <0.001		
Roden, 2013[139]	Grp1: Sitagliptin Fixed (100mg) Grp2: Empagliflozin Fixed (10 mg) ITT: Yes Followup (wks): 24	Grp1: B: 7.85 (0.79) F: 7.2 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Grp2: B: 7.87 (0.85) F: 7.21 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Between-group difference: Grp2: 0 (-0.15-0.14) p 0.9697	Grp1: B: 79.3 (20.4) F: 79.48 (76.78-82.18) F-B: 0.18 (-0.16-0.52) Grp2: B: 77.8 (18) F: 75.32 (76.78-82.18) F-B: -2.48 (-2.82--2.14) Between-group difference: Grp2: -2.67 (-3.15--2.18) p <0.0001	Grp1: B: 132.5 (15.8) F: 132.7 (130.4-135) F-B: 0.5 (-1.1-2.1) Grp2: B: 133 (16.6) F: 129.5 (130.4-135) F-B: -2.9 (-4.5-1.3) Between-group difference: Grp2: -3.4 (-5.7-1.2) p 0.0031	Grp1: F-B: 0.22 (9.53) Grp2: F-B: 0.02 (8.77)
Roden, 2013[139]	Grp1: Sitagliptin Fixed (100mg) Grp2: Empagliflozin Fixed (25 mg) ITT: Yes Followup (wks): 24	Grp1: B: 7.85 (0.79) F: 7.2 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Grp2: B: 7.86 (0.88) F: 7.2 (7.08-7.33) F-B: -0.78 (-0.88-0.67)	Grp1: B: 79.3 (20.4) F: 79.48 (76.78-82.18) F-B: 0.18 (-0.16-0.52) Grp2: B: 78.4 (18.7) F: 76.08 (76.78-82.18) F-B: -2.26 (-2.6--1.92) Between-group difference:	Grp1: B: 132.5 (15.8) F: 132.7 (130.4-135) F-B: 0.5 (-1.1-2.1) Grp2: B: 129.9 (17.5) F: 126.7 (130.4-135) F-B: -3.7 (-5.3-2.1) Between-group difference:	Grp1: F-B: 0.22 (9.53) Grp2: F-B: -0.25 (8.63)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Between-group difference: Grp2: -0.12 (-0.26-0.03) p 0.106	Grp2: -2.45 (-2.93--1.96) p <0.0001	Grp2: -4.2 (-6.5-2) p 0.0003	
Roden, 2013[139]	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (25 mg) ITT: Yes Followup (wks): 24	Grp1: B: 7.85 (0.79) F: 7.2 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Grp2: B: 7.86 (0.88) F: 7.2 (7.08-7.33) F-B: -0.78 (-0.88-0.67) Between-group difference: Grp2: -0.12 (-0.26-0.03) p 0.106	Grp1: B: 79.3 (20.4) F: 79.48 (76.78-82.18) F-B: 0.18 (-0.16-0.52) Grp2: B: 78.4 (18.7) F: 76.08 (76.78-82.18) F-B: -2.26 (-2.6--1.92) Between-group difference: Grp2: -2.45 (-2.93--1.96) p <0.0001	Grp1: B: 132.5 (15.8) F: 132.7 (130.4-135) F-B: 0.5 (-1.1-2.1) Grp2: B: 129.9 (17.5) F: 126.7 (130.4-135) F-B: -3.7 (-5.3-2.1) Between-group difference: Grp2: -4.2 (-6.5-2) p 0.0003	Grp1: F-B: 0.22 (9.53) Grp2: F-B: 0.02 (8.77)
Roden, 2013[139]	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (10 mg) ITT: Yes Followup (wks): 24	Grp1: B: 7.85 (0.79) F: 7.2 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Grp2: B: 7.87 (0.85) F: 7.21 (7.08-7.33) F-B: -0.66 (-0.76-0.56) Between-group difference: Grp2: 0 (-0.15-0.14) p 0.9697	Grp1: B: 79.3 (20.4) F: 79.48 (76.78-82.18) F-B: 0.18 (-0.16-0.52) Grp2: B: 77.8 (18) F: 75.32 (76.78-82.18) F-B: -2.48 (-2.82--2.14) Between-group difference: Grp2: -2.67 (-3.15--2.18) p <0.0001	Grp1: B: 132.5 (15.8) F: 132.7 (130.4-135) F-B: 0.5 (-1.1-2.1) Grp2: B: 133 (16.6) F: 129.5 (130.4-135) F-B: -2.9 (-4.5-1.3) Between-group difference: Grp2: -3.4 (-5.7-1.2) p 0.0031	Grp1: F-B: 0.22 (9.53) Grp2: F-B: -0.25 (8.63)
Rosenstock, 2006[140]	Grp1: Metformin Varied, glucose: Mean daily glucose <= 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Rosiglitazone	Grp1 B: 8.8 (1.0) F: 7.0 (1.0) F-B: -1.8 Grp2 B: 8.8 (1.0) F: 7.2 (1.0)	Grp1 F-B: Median: -2.2 (IQR: -5.5, -0.5) Grp2 F-B: Median: 1.7 (IQR: -1.2,		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Varied, glucose: Mean daily glucose <= 6.1 mmol/l Start: 4 mg, Max: 8 mg, Mean: 7.7 mg D: 32 wks	F-B: -1.6 Grp1-Grp2: -0.2 (SE 0.20)	- 4.5)		
Rosenstock, 2006[140]	Grp1: Metformin Varied, mean daily glucose <= 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 D: 32 wks Grp2: Metformin + rosiglitazone Varied, mean daily glucose <= 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1799 mg; Start: 2 mg, Max: 8 mg, Mean: 7.2 mg D: 32 wks	Grp1 B: 8.8 (1.0) F: (1.0) F-B: -1.8 Grp2 B: 8.9 (1.1) F: 6.6 (1.0) F-B: -2.3 Grp1-Grp2: 0.5 (SE: 0.20) p: 0.008	Grp1 F-B: Median: -2.2 (IQR: -5.5, -0.5) Grp2 F-B: Median: 0.05 (IQR: -3.45, 3)		
Rosenstock, 2010[141]	Grp1: Pioglitazone + placebo Fixed (30mg qd) Grp2: Alogliptin + placebo Fixed (25mg qd) ITT: Yes Followup (wks): 26	Grp1: B: 8.76 (1.005) F-B: -1.15 (0.083) Grp2: B: 8.8 (0.988) F-B: -0.96 (0.081	Grp1: F-B: 2.19 (0.302) Grp2: F-B: -0.29 (0.291)		
Rosenstock, 2012[142]	Grp1: Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2: Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day) ITT: Yes Followup (wks): 12	Grp1: B: 7.75 (0.83) F: 7.5 (0.96) F-B: -0.22 (0.702) Grp2: B: 7.83 (0.96) F: 7.1 (0.85) F-B: -0.76 (0.992) Between-group difference: p <0.001	Grp1: B: 85.5 (19.58) F-B: -1.1 (2.4) Grp2: B: 87.7 (15.49) F-B: -2.6 (2.3) Between-group difference: p <0.001	Grp1: B: 125.2 (9.8) F-B: -1.3 (1.5) Grp2: B: 128.7 (13.4) F-B: -0.8 (1.4)	Grp1: B: 69.9 (12) F-B: 1.7 (1.2) Grp2: B: 71 (12.4) F-B: -0.2 (1.1)
Rosenstock, 2012[142]	Grp1: Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2: Metformin + canagliflozin Fixed (Mean: 1904 mg/day) Fixed (200 mg/day)	Grp1: B: 7.75 (0.83) F: 7.5 (0.96) F-B: -0.22 (0.702) Grp2:	Grp1: B: 85.5 (19.58) F-B: -1.1 (2.4) Grp2: B: 87.7 (17.22)	Grp1: B: 125.2 (9.8) F-B: -1.3 (1.5) Grp2: B: 126.5 (13.3)	Grp1: B: 69.9 (12) F-B: 1.7 (1.2) Grp2: B: 70.8 (9.9)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	ITT: Yes Followup (wks): 12	B: 7.61 (0.8) F: 6.9 (0.68) F-B: -0.7 (0.72) Between-group difference: p <0.001	F-B: -2.7 (3) Between-group difference: p <0.001	F-B: 1 (1.3)	F-B: 0.6 (1)
Rosenstock, 2012[142]	Grp1: Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2: Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) ITT: Yes Followup (wks): 12	Grp1: B: 7.75 (0.83) F: 7.5 (0.96) F-B: -0.22 (0.702) Grp2: B: 7.64 (0.95) F: 6.88 (0.919) F-B: -0.74 (0.615) Between-group difference: p <0.001	Grp1: B: 85.5 (19.58) F-B: -1.1 (2.4) Grp2: B: 87 (18) F-B: -0.6 (3) Between-group difference: p NS	Grp1: B: 125.2 (9.8) F-B: -1.3 (1.5) Grp2: B: 124.3 (11.1) F-B: -2.1 (1.8)	Grp1: B: 69.9 (12) F-B: 1.7 (1.2) Grp2: B: 72.9 (10.8) F-B: -1.7 (0.9)
Rosenstock, 2012[142]	Grp1: Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2: Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT: Yes Followup (wks): 12	Grp1: B: 7.75 (0.83) F: 7.5 (0.96) F-B: -0.22 (0.702) Grp2: B: 7.69 (1.02) F: 6.8 (0.82) F-B: -0.92 (0.695) Between-group difference: p <0.001	Grp1: B: 85.5 (19.58) F-B: -1.1 (2.4) Grp2: B: 87.8 (15.79) F-B: -3.4 (2.8) Between-group difference: p <0.001	Grp1: B: 125.2 (9.8) F-B: -1.3 (1.5) Grp2: B: 126.1 (11.6) F-B: -4.9 (1.5)	Grp1: B: 69.9 (12) F-B: 1.7 (1.2) Grp2: B: 72.6 (10.5) F-B: -1.7 (1.2)
Rosenstock, 2012[142]	Grp1: Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2: Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT: Yes Followup (wks): 12	Grp1: B: 7.64 (0.95) F: 6.88 (0.919) F-B: -0.74 (0.615) Grp2: B: 7.69 (1.02) F: 6.8 (0.82) F-B: -0.92 (0.695) Between-group difference: p <0.001	Grp1: B: 87 (18) F-B: -0.6 (3) Grp2: B: 87.8 (15.79) F-B: -3.4 (2.8) Between-group difference: p NS p <0.001	Grp1: B: 128.7 (13.4) F-B: -0.8 (1.4) Grp2: B: 126.1 (11.6) F-B: -4.9 (1.5)	Grp1: B: 72.9 (10.8) F-B: -1.7 (0.9) Grp2: B: 72.6 (10.5) F-B: -1.7 (1.2)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		p <0.001			
Rosenstock, 2012[142]	Grp1: Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2: Metformin + canagliflozin Fixed (Mean: 1904 mg/day) Fixed (200 mg/day) ITT: Yes Followup (wks): 12	Grp1: B: 7.64 (0.95) F: 6.88 (0.919) F-B: -0.74 (0.615) Grp2: B: 7.61 (0.8) F: 6.9 (0.68) F-B: -0.7 (0.72) Between-group difference: p <0.001 p <0.001	Grp1: B: 87 (18) F-B: -0.6 (3) Grp2: B: 87.7 (15.49) F-B: -2.6 (2.3) Between-group difference: p NS p <0.001	Grp1: B: 128.7 (13.4) F-B: -0.8 (1.4) Grp2: B: 124.3 (11.1) F-B: -2.1 (1.8)	Grp1: B: 72.9 (10.8) F-B: -1.7 (0.9) Grp2: B: 70.8 (9.9) F-B: 0.6 (1
Rosenstock, 2012[142]	Grp1: Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2: Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day) ITT: Yes Followup (wks): 12	Grp1: B: 7.64 (0.95) F: 6.88 (0.919) F-B: -0.74 (0.615) Grp2: B: 7.83 (0.96) F: 7.1 (0.85) F-B: -0.76 (0.992) Between-group difference: p <0.001 p <0.001	Grp1: B: 87 (18) F-B: -0.6 (3) Grp2: B: 87.7 (17.22) F-B: -2.7 (3) Between-group difference: p NS p <0.001	Grp1: B: 128.7 (13.4) F-B: -0.8 (1.4) Grp2: B: 126.5 (13.3) F-B: 1 (1.3)	Grp1: B: 72.9 (10.8) F-B: -1.7 (0.9) Grp2: B: 71 (12.4) F-B: -0.2 (1.1)
Rosenstock, 2013[144]	Grp1: Metformin + placebo Not specified Grp2: Metformin + sitagliptin Not specified Fixed (100mg) ITT: Yes Followup (wks): 12	Grp1: F-B: 0.15 (0-0.3) Grp2: F-B: -0.45 (-0.65-0.25) p Between-group difference: p <0.0001	Grp1: F-B: -1.2 (-1.8--0.5) Grp2: F-B: -2.7 (-3.4--2.1) Between-group difference:p p på‰¤0.001	Grp1: F-B: -2.23 (14.84) Grp2: F-B: -8.52 (23.83)	
Rosenstock, 2013[144]	Grp1: Metformin + placebo Not specified Grp2: Metformin + empagliflozin Not specified Fixed (10mg) ITT: Yes	Grp1: F-B: 0.15 (0-0.3) p Grp2: F-B: -0.56 (-0.71-0.41) p Between-group	Grp1: F-B: -1.2 (-1.8--0.5) Grp2: F-B: -2.6 (-3.2--2) Between-group difference:	Grp1: F-B: -2.23 (14.84) Grp2: F-B: -4.39 (13.09	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Followup (wks): 12	difference: p <0.0001	p pâ‰¤0.001		
Rosenstock, 2013[144]	Grp1: Metformin + placebo Not specified Grp2: Metformin + empagliflozin Not specified Fixed (25mg) ITT: Yes Followup (wks): 12	Grp1: F-B: 0.15 (0-0.3) Grp2: F-B: -0.55 (-0.7-0.4) Between-group difference: p <0.0001	Grp1: F-B: -1.2 (-1.8--0.5) Grp2: F-B: -0.8 (-1.5--0.2) Between-group difference:	Grp1: F-B: -2.23 (14.84) Grp2: F-B: -1.79 (11.65)	
Rosenstock, 2013[144]	Grp1: Metformin + sitagliptin Not specified Fixed (100mg) Grp2: Metformin + empagliflozin Not specified Fixed (25mg) ITT: Yes Followup (wks): 12	Grp1: F-B: -0.45 (-0.65-0.25) Grp2: F-B: -0.55 (-0.7-0.4) Between-group difference: p <0.0001 p <0.0001	Grp1: F-B: -0.8 (-1.5--0.2) Grp2: F-B: -2.6 (-3.2--2) Between-group difference: p pâ‰¤0.001	Grp1: F-B: -1.79 (11.65) Grp2: F-B: -4.39 (13.09)	
Rosenstock, 2013[144]	Grp1: Metformin + sitagliptin Not specified Fixed (100mg) Grp2: Metformin + empagliflozin Not specified Fixed (10mg) ITT: Yes Followup (wks): 12	Grp1: F-B: -0.45 (-0.65-0.25) Grp2: F-B: -0.56 (-0.71-0.41) Between-group difference: p <0.0001 p <0.0001	Grp1: F-B: -0.8 (-1.5--0.2) Grp2: F-B: -2.7 (-3.4--2.1) Between-group difference: p pâ‰¤0.001		
Rosenstock, 2015[145]	Grp1: Metformin + saxagliptin + placebo Not specified (1500-2000 mg/d) Fixed 5 mg/d Grp2: Metformin + dapagliflozin + placebo Not specified (1500-2000 mg/d) Fixed 10 mg/d	Grp1: B: 9.03 (1.05) F: NR Grp2: B: 8.87 (1.17) F: NR	Grp1: B: 88 (18.7) F: NR Grp2: B: 86.3 (18.6) F: NR	Grp1: B: 128 (12.5) F: NR Grp2: B: 130 (14.1) F: NR	
Ross, 2012[146]	Grp1: Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2: Metformin + linagliptin + placebo	Grp1: B: 7.92 (0.74) F-B: 0.28 (0.11) Grp2:	Grp1: B: 77.7 (19.4) F-B: -1.1 (1.9) Grp2:	Grp1: F-B: -1.79 (11.65) Grp2: F-B: -8.52 (23.83)	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT: No Followup (wks): 12	B: 7.98 (0.72) F-B: -0.52 (0.05) Between-group difference: Grp2: -0.8 (-1.02-0.58) p <0.0001	B: 80.6 (17.5) F-B: -1 (2.2)		
Russell-Jones, 2012[147]	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Exenatide + placebo Not specified ITT: No Followup (wks): 26	Grp1: B: 8.6 (1.2) F: 6.99 (0.07) F-B: -1.48 (0.07) Grp2: B: 8.5 (1.2) F: 6.94 (0.07) F-B: -1.43 (0.07) Between-group difference: Grp1: (-0.26-0.17) p 0.62	Grp1: B: 85.9 (19.6) F-B: -2 (0.2) Grp2: B: 87.5 (18.9) F-B: -2 (0.2) Between-group difference: p 0.892	Grp1: F-B:p Grp2: F-B: -1.3 (0.8)	Grp1: F-B: 0.3 (9.5) Grp2: F-B: 1.5 (10)
Russell-Jones, 2012[147]	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Sitagliptin + placebo Not specified ITT: No Followup (wks): 26	Grp1: B: 8.6 (1.2) F: 6.99 (0.07) F-B: -1.48 (0.07) Grp2: B: 8.5 (1.3) F: 7.32 (0.08) F-B: -1.15 (0.08) Between-group difference: Grp1: (-0.26-0.17) p 0.62 Grp2: (-0.62-0.13) p <0.001	Grp1: B: 85.9 (19.6) F-B: -2 (0.2) Grp2: B: 86.1 (17.8) F-B: 1.5 (0.3) Between-group difference: p 0.892 p <0.001	Grp1: F-B:p Grp2: F-B: -1.8 (1)	Grp1: F-B: 0.3 (9.5) Grp2: F-B: 0.5 (9.7)
Russell-Jones, 2012[147]	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) ITT: No	Grp1: B: 8.6 (1.2) F: 6.99 (0.07) F-B: -1.48 (0.07) Grp2: B: 8.5 (1.2) F: 6.84 (0.08)	Grp1: B: 85.9 (19.6) F-B: -2 (0.2) Grp2: B: 88.7 (18.7) F-B: -0.8 (0.3) Between-group	Grp1: F-B:p Grp2: F-B: -1.7 (1)	Grp1: F-B: 0.3 (9.5) Grp2: F-B: -1.7 (8.7)

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Followup (wks): 26	F-B: -1.63 (0.08) Between-group difference: Grp1: (-0.26-0.17) p 0.62 Grp2: (-0.15-0.35) p 0.328	difference: p 0.892 p <0.001		
Russell-Jones, 2012[147]	Grp1: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2: Sitagliptin + placebo Not specified ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.2) F: 6.84 (0.08) F-B: -1.63 (0.08) Grp2: B: 8.5 (1.3) F: 7.32 (0.08) F-B: -1.15 (0.08) Between-group difference: Grp1: (-0.15-0.35) p 0.328 Grp2: (-0.62-0.13) p <0.001	Grp1: B: 86.1 (17.8) F-B: 1.5 (0.3) Grp2: B: 87.5 (18.9) F-B: -2 (0.2) Between-group difference: p <0.001	Grp1: F-B: -1.7 (1) Grp2: F-B: -1.3 (0.8)	Grp1: F-B: -1.7 (8.7) Grp2: F-B: 1.5 (10)
Russell-Jones, 2012[147]	Grp1: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2: Exenatide + placebo Not specified ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.2) F: 6.84 (0.08) p F-B: -1.63 (0.08) p Grp2: B: 8.5 (1.2) F: 6.94 (0.07) p F-B: -1.53 (0.07) p Between-group difference: Grp1: 0.1 (-0.15-0.35) p 0.328	Grp1: B: 86.1 (17.8) F-B: 1.5 (0.3) Grp2: B: 88.7 (18.7) F-B: -0.8 (0.3) Between-group difference: p <0.001 p <0.001	Grp1: F-B: -1.7 (1) Grp2: F-B: -1.8 (1)	Grp1: F-B: -1.7 (8.7) Grp2: F-B: 0.5 (9.7)
Russell-Jones, 2012[147]	Grp1: Sitagliptin + placebo Not specified Grp2: Exenatide + placebo Not specified ITT: No Followup (wks): 26	Grp1: B: 8.5 (1.3) F: 7.32 (0.08) F-B: -1.15 (0.08) Grp2: B: 8.5 (1.2)	Grp1: B: 88.7 (18.7) F-B: -0.8 (0.3) Grp2: B: 87.5 (18.9) F-B: -2 (0.2)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		F: 6.94 (0.07) F-B: -1.53 (0.07) Between-group difference: Grp1: 0.38 (-0.62-0.13) p <0.001	Between-group difference: p <0.001		
Russell-Jones, 2012[147]	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Exenatide + placebo Not specified ITT: No Followup (wks): 26			Grp1: F-B: -1.8 (1) Grp2: F-B: -1.3 (0.8)	
Schernthaner, 2015[148]	Grp1: Metformin + glimepiride + placebo Mean Dose: 1572 mg/d Titrated (Mean: 3.3 mg/d Max: 6mg/d) Grp2: Metformin + saxagliptin + placebo Mean Dose: 1647 Fixed (5mg/d) ITT: No Followup (wks): 52	Grp1 B: NR F: -0.57 (NR) Grp2 B: NR F: -0.46 (NR)	Grp1 B: NR F: 1 (NR) Grp2 B: NR F: -0.8 (NR)		
Schernthaner, 2015[148]	Grp1: Metformin + glimepiride + placebo Mean Dose: 1572 mg/d Titrated (Mean 3.3 mg/d Max: 6mg/d) Grp2: Metformin + saxagliptin + placebo Mean Dose: 1647 Fixed (5mg/d) ITT: No Followup (wks): 52	Grp1 B: NR F: -0.64 (NR) Grp2 B: NR F: -0.44 (NR)			
Schernthaner, 2015[148]	Grp1: Metformin + glimepiride + placebo Mean Dose: 1572 mg/d Titrated (Mean 3.3 mg/d Max: 6mg/d) Grp2: Metformin + saxagliptin + placebo Mean Dose: 1647 Fixed (5 mg/d)	Grp1 B: NR F: -0.74 (NR) Grp2 B: NR F: -0.4 (NR)			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	ITT: No Followup (wks): 52				
Schernthaner, 2004[149]	Grp1: Metformin Varied Start: 850 mg up to 3 times/day, Max: 2550 mg Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1 B: 8.68 (0.98) F: 7.18 F-B: -1.5 Grp2 B: 8.69 (1.02) F: 7.28 F-B: -1.41 Grp1-Grp2: -0.09	Grp1 F-B: 1.9 Grp2 F-B: -2.5 Grp1-Grp2: 4.4		Grp1: F-B: 0.5 (9.7) Grp2: F-B: 1.5 (10
Schondorf, 2011[150]	Grp1: Metformin + pioglitazone + placebo Fixed (1700 mg) Fixed (30 mg) Grp2: Metformin + glimepiride Fixed (1700 mg) Fixed (2 mg) ITT: NR Followup (wks): 24	Grp1: B: 7.4 (0.8) F: 6.6 (0.9) F-B:p <0.05 Grp2: B: 6.7 (0.5) F: 6 (0.5) p F-B:p <0.05 Between-group difference: p NS	Grp1: F-B: -0.24 (4.99) p NS Grp2: F-B: 0.1 (3.21) p NS		
Schumm-Draeger, 2015[151]	Grp1: Metformin + placebo Fixed (adjusted to 1500, 2000 or 2500 mg/d) Grp2: Metformin + dapagliflozin Fixed 5mg twice daily	Grp1: B: 7.94 (0.852) F: 7.59 (0.895) Grp2: B: 7.79 (0.764) F: 7.15 (0.704)	Grp1: B: 88.82 (15.327) F: 87.89 (15.474) Grp2: B: 93.62 (16.641) F: 90.82 (17.07)	Grp1: B: 133.4 (11.87) F: 131.6 (11.77) Grp2: B: 130.3 (11.38) F: 126.6 (11.92)	
Schumm-Draeger, 2015[151]	Grp1: Metformin + placebo Fixed (adjusted to 1500, 2000, 2500 mg/d) Grp2: Metformin + dapagliflozin Fixed 10 mg/d	Grp1: B:7.94 (0.852) F: 7.59 (0.895) Grp2: B: 7.71 (0.713) F: 7.16 (0.625)	Grp1: B: 88.82 (15.327) F: 87.89 (15.474) Grp2: B: 90.58 (15.929) F: 88.17 (16.195)	Grp1: B: 133.4 (11.87) F: 131.6 (11.77) Grp2: B: 132.3 (12.04) F: 128.3 (13.47)	
Scott, 2007[152]	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks Grp2: Sitagliptin	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62)	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed Start: 100 mg, Max: 100 mg	Grp2 B: 7.83 (0.95) F: 7.34 (1.01) F-B: -0.54 (CI: -0.68, -0.4) Grp1-Grp2: -0.22			
Scott, 2007[152]	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks Grp2: Sitagliptin Fixed Start: 50 mg, Max: 50 mg	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62) Grp2 B: 7.89 (0.94) F: 7.5 (1.14) F-B: -0.43 (CI: -0.56, -0.29) Grp1-Grp2: -0.33	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change		
Scott, 2007[152]	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks Grp2: Sitagliptin Fixed Start: 25 mg, Max: 25 mg	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62) Grp2 B: 7.85 (0.88) F: 7.48 (0.98) F-B: -0.41 (CI: -0.55, -0.27) Grp1-Grp2: -0.35	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change		
Scott, 2007[152]	Grp1: Glipizide Varied, glucose: <160mg/dl Start: 5mg, Max: 20mg D: 6 wks Grp2: Sitagliptin Fixed Start: 10, Max: 10	Grp1 B: 7.82 (0.95) F: 7.11 (0.91) F-B: -0.76 (CI: -0.9, -0.62) Grp2 B: 7.89 (0.94) F: 7.77 (1.22) F-B: -0.15 (CI: -0.29, -0.01) Grp1-Grp2: -0.61	Grp1 F-B: 0.9 (CI: 0.5, 1.3) Grp2 F-B: no significant weight change		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Scott, 2008[153]	Grp1: Metformin Fixed Start: >1500 mg Grp2: Metformin + rosiglitazone Fixed Start: >1500 mg; Start: 8 mg, Mean: 8 mg	Grp1 B: 7.68 (0.88) F: 7.47 (1.05) F-B: -0.22 (CI: -0.36, -0.08) Grp2 B: 7.73 (0.88) F: 6.94 (0.75) F-B: -0.79 (CI: -0.92, -0.65) Grp1-Grp2: 0.57 (CI: 0.37, 0.76)	Grp1 F-B: -0.8 (CI: -1.2, -0.4) Grp2 F-B: 1.5 (CI: 1.0, 1.9) Grp2-Grp1: 2.3 (CI: 1.7, -2.9)		
Scott, 2008[153]	Grp1: Metformin Fixed Total starting dose: > 1500 mg Grp2: Metformin + sitagliptin Fixed Total starting dose: > 1500 mg; Start: 100 mg, Mean: 100 mg	Grp1 B: 7.68 (0.88) F: 7.47 (1.05) F-B: -0.22 (CI: -0.36, -0.08) Grp2 B: 7.75 (0.99) F: 7.01 (0.86) F-B: -0.73 (CI: -0.87, -0.6) Grp1-Grp2: -0.51 (CI: -0.7, -0.32) p: <0.001	Grp1 F-B: -0.8 (CI: -1.2, -0.4) Grp2 F-B: -0.4 (CI: -0.8, 0) Grp1-Grp2: -0.4		
Scott, 2008 [153]	Grp1: Metformin + rosiglitazone NR; Fixed Start: >=1500 mg; Mean: 8 mg D: 10 wks; NA Grp2: Metformin + sitagliptin Fixed Start: > 1500 mg; Start: 100 mg, Mean: 100 mg	Grp1-Grp2: -0.06 (CI: -0.25, 0.14)	Grp1 F-B: 1.5 (CI: 1, 1.9) Grp2 F-B: -0.4 (CI: -0.8, 0) Grp1-Grp2: 1.9 (CI: 1.3, 2.5)		
Seck, 2010[154]	Grp1: Metformin + glipizide Fixed NR; Start: 5, Max: 20, Mean: 9.2 mg D: 2 Years Grp2: Metformin + sitagliptin Fixed NR	Grp1 F-B: -0.35 (CI: -0.44, -0.26) Grp2 F-B: -0.33 (CI: -42, -0.25) Grp1-Grp2: -0.01 (CI: -	Grp1 F-B: 0.7 (CI: 0, 1.3) p: NS Grp2 F-B: -1.6 (CI: -2.3, -1) p: NS Grp1-Grp2: 2.3 (1.6, 3)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	D: 2 Years	0.1, 0.08)	p: NS		
Seino, 2010[155]	Grp1: Glibenclamide Varied, prespecified target dose Start: 1.25 mg, Max: 2.5 mg D: 4 Wks Grp2: Liraglutide Varied, prespecified target dose Start: 0.3 mg, Max: 0.9 mg D: 2 Wks	Grp1 F-B: -1.88 (SE: 0.07) p: <0.0001 Grp2 F-B: -1.38 (SE: 0.09) p:<0.0001 Grp1-Grp2: 0.5 (CI: 0.3, 0.7) p<0.0001	Grp1 F-B: -0.92 (2.15) p: p<0.0001 Grp2 F-B: 0.99 (1.84) p: p<0.0001 Grp1-Grp2: 1.91 (CI: 1.48, 2.34) p: <0.0001		
Seino, 2012[156]	Grp1: Metformin + placebo Fixed (500mg/day, or 750mg/day) Grp2: Metformin + alogliptin Fixed (500mg/day, or 750mg/day) Fixed (25mg) ITT: Yes Followup (wks): 12	Grp1: B: 8 (0.86) F-B: 0.21 (0.64) (0.11-0.33) p Grp2: B: 8.02 (0.73) F-B: -0.64 (0.49) (-0.75-0.53) p	Grp1: B: 69.89 (14.23) F-B: -0.23 (1.37) Grp2: B: 69.47 (12.46) F-B: 0.17 (1.38)		
Seino, 2012[156]	Grp1: Metformin + placebo Fixed (500mg/day, or 750mg/day) Grp2: Metformin + alogliptin Fixed (500mg/day, or 750mg/day) Fixed (12.5mg) ITT: Yes Followup (wks): 12	Grp1: B: 8 (0.86) F-B: 0.21 (0.64) (0.11-0.33) p Grp2: B: 7.89 (0.82) F-B: -0.54 (0.56) (-0.67-0.44) p	Grp1: B: 69.89 (14.23) F-B: -0.23 (1.37) Grp2: B: 69.65 (12.67) F-B: -0.09 (1.29)		
Shihara, 2011[157]	Grp1: Pioglitazone Titrated (Mean: 23.24 mgMax: 30mg for women-45mg for menstarting 15mg/d) Grp2: SU Titrated (Mean: 23.24Max: 6mg/dstarting 0.5mg/d) ITT: No Followup (wks): 24	Grp1: B: 7.8 (0.9) F: 7.2 (0.8) F-B: -0.85 (1) p <0.001 Grp2: B: 7.8 (0.9) F: 6.8 (0.7) pNS F-B: -0.98 (0.75) p <0.001 Between-group difference: p 0.31	Grp1: B: 65.5 (15.1) F: 66.2 (14.4) p F-B:p ns Grp2: B: 66 (12) F: 66.4 (11.7) p F-B:p 0.036 Between-group difference: p NS		
Srivastava,	Grp1: Metformin + glimepiride	Grp1:			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2012[158]	Fixed (kept at starting dose (dose on prior to study)) Titrated (Max: 4 mg/daystarted at 1-2 mg/day) Grp2: Metformin + sitagliptin Fixed (metformin dose prior to the study kept constant) Titrated (Max: 200 mg/daystarted at 50/100 mg/day) ITT: Yes Followup (wks):	B: 8.25 (0.57) F: 7.08 (0.36) F-B: -1.17 (0.25) p <0.001 Grp2: B: 8.28 (0.42) F: 7.64 (0.42) F-B: -0.64 (0.99) p <0.001 Between-group difference: p <0.001			
Suzuki, 2014[161]	Grp1: Sitagliptin Fixed 50 mg/d Grp2: Liraglutide Titrated 0.9 mg/d	Grp1: B: 9.1 (1.6) F: 8 (1.4) Grp2: B: 9.8 (2.2) F: 7.4 (1.7)	Grp1: B: 81.7 (25.4) F: 80.2 (25.1) Grp2: B: 82.3 (19) F: 79.3 (19.2)	Grp1: B: 136.7 (19.3) F: 135.1 (17.3) Grp2: B: 138 (20.5) F: 129.5 (16.2)	
Tan, 2004[162]	Grp1: Pioglitazone Varied Start: 30 mg, Max: 45 mg Grp2: Glibenclamide Varied Start: 1.75 mg, Max: 10.5 mg	Grp1 B: 8.4 (0.7) F: 7.9 F-B: -0.5 p: <0.005 Grp2 B: 8.5 (0.8) F: 8.1 F-B: -0.4 p: <0.005 Grp1-Grp2: -0.1	Grp1 B: 86.2 (15.6) F: 91.2 F-B: 5 (CI: 3.7, 6.2) p: <0.05 Grp2 B: 85.1 (13.6) F: 88.5 F-B: 3.4 (CI: 2.7, 4.1) p: <0.05 Grp1-Grp2: 1.6		
Tan, 2004[162]	Grp1: Pioglitazone Varied Start: 15 mg, Max: 45 mg Grp2: Glimepiride Varied Start: 2 mg, Max: 8 mg	Grp1 B: 8.54 (0.903) F: 7.76 F-B: -0.78 (0.162) p: <0.001 Grp2 B: 8.45 (1.02) F: 7.77 F-B: -0.68 (0.169) p: <0.001	Grp1 B: 88.7 (17.4) F: 91.7 F-B: 3 p: <0.001 Grp2 B: 89.1 (16) F: 90.2 F-B: 1.1 p: 0.008 Grp1-Grp2: 1.9 p: 0.002		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
		Grp1-Grp2: -0.1 p: 0.638			
Taskinen, 2011[164]	Grp1: Metformin + placebo Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Grp2: Metformin + linagliptin Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Fixed (5mg) ITT: No Followup (wks): 24	Grp1: B: 8.02 (0.07) F-B: 0.15 (0.06) Grp2: B: 8.09 (0.04) F-B: -0.49 (0.04) Between-group difference: Grp2: -0.64 0.07 (-0.78-0.5) p <0.0001	Grp1: B: 83.3 (16.6) F-B: -0.5 Grp2: B: 82.2 (17.2) F-B: -0.4		
Taslimi, 2013[165]	Grp1: Metformin Fixed (1000mg) Grp2: Pioglitazone Fixed (30mg) ITT: Yes Followup (wks): 12	Grp1: B: 8.4 (1.5) F: 7 (1.4) F-B:p <0.01 Grp2: B: 8.2 (1.8) F: 7.3 (1.6) F-B:p <0.05			
Teramoto, 2007[166]	Grp1: Pioglitazone Varied, glucose: <= 126 mg/dL Start: 15 mg, Max: 30 mg D: 15 wks Grp2: Glibenclamide Varied, glucose: <= 126 mg/dL Start: 1.25 mg, Max: 2.5 mg D: 15 wks	Grp1 F-B: -0.8 (1.14) p: <0.05 Grp2 F-B: -1.43 (1.09) p: <0.05 Grp1-Grp2: 0.63 (SE: 0.48)			
Tosi, 2003[167]	Grp1: Metformin Varied Start: 500 mg, Max: 3000 mg Grp2: Glibenclamide Varied Start: 5 mg, Max: 15 mg	Grp1 B: 7.7 (1.4) F: 7.3 F-B: -0.4 Grp2 B: 7.85 (1.4) F: 7.4 F-B: -0.45 Grp1-Grp2: 0.05			

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Tosi, 2003[167]	Grp1: Metformin Varied Start: 500 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Varied Start: 400 mg, Max: 2400 mg; Start: 2.5 mg, Max: 15 mg	Grp1 B: 7.8 (1.4) F: 7.3 F-B: -0.5 Grp2 B: 7.8 (1.0) F: 5.9 F-B: -1.9 Grp1-Grp2: 1.4			
Turkmen Kemal, 2007[168]	Grp1: Metformin Fixed Start: 1700 mg D: 6 mos Grp2: Rosiglitazone Fixed Start: 8 mg	Grp1 B: 5.95 Range: 5.6 F: 5.85 Range: 1.9 Grp2 B: 6 Range: 2.4 F: 5.95 Range: 1.9			
Turner, 1999[169]	Grp1: Metformin Varied, glucose: FPG <6 mmol/L Max: 2550 mg/day D: 9 yrs Grp2: Any in the Sulfonylurea class Varied, glucose: 6 mmol/L Max: Chlorpropramide-500 mg; Glyburide 20 mg D: 9 yrs	Grp1 Proportion achieving HbA1c<7% at 3 yrs: 44 (CI: 42, 46) 6 yrs: 34 (CI: 32, 37) 9 yrs: (CI: 11, 15) Grp2 Proportion achieving HbA1c<7% at 3 yrs: 45 (CI: 43, 48) 6 yrs: 28 (CI: 26, 30) 9 yrs: (CI: 19, 23)			
Umpierrez, 2006[170]	Grp1: Metformin + pioglitazone NR; Varied, glucose: <120 mg/dL, HbA1c: <8.0% Start: 1.54 g, Max: 1.57g; Start: 30 mg, Max: 45 mg D: NR; Unclear Grp2: Metformin + glimepiride NR; Glucose: <120 mg/dL Start: 1.47 g, Max: 1.49 g; Start: 2 mg, Max: 8 mg D: NR; 6 wks	Grp1 F-B: -1.23 (SE: 0.073) p: 0.4825 Grp2 F-B: -1.3 (SE: 0.077) Grp1-Grp2: 0.07 (SE: 0.11)	Grp1 F-B: 1.85 (SE: 0.38) Grp2 F-B: 1.74 (SE: 0.41) Grp1-Grp2: 0.11		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Umpierrez, 2014[171]	Grp1: Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2: Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 0.75mg) ITT: Yes Followup (wks):	Grp1: B: 7.6 (0.8) F-B: -0.51 (0.07) Grp2: B: 7.6 (0.9) F-B: -0.55 (0.07)	Grp1: B: 92 (19) F-B: -2.3 (0.24) Grp2: B: 92 (19) F-B: -0.8 (0.24)	Grp1: B: 129 (16) F-B: -1 (0.88) Grp2: B: 130 (16) F-B: -0.1 (0.88)	Grp1: F-B: 1.1 (0.57) Grp2: F-B: 1.6 (0.57
Umpierrez, 2014[171]	Grp1: Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2: Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 1.5mg) ITT: Yes Followup (wks):	Grp1: B: 7.6 (0.8) F-B: -0.51 (0.07) Grp2: B: 7.6 (0.9) F-B: -0.7 (0.07)	Grp1: B: 92 (19) F-B: -2.3 (0.24) Grp2: B: 93 (19) F-B: -1.6 (0.24	Grp1: B: 129 (16) F-B: -1 (0.88) Grp2: B: 130 (16) F-B: -2.7 (0.88	Grp1: F-B: 1.1 (0.57) Grp2: F-B: 1.8 (0.57)
van der Meer, 2009[172]	Grp1: Metformin + glimepiride Fixed; Varied Start: 1000 mg, Max: 2000 mg; NR D: NR; 8 wks Grp2: Pioglitazone + glimepiride Fixed; Varied Start: 15 mg, Max: 30 mg; NR D: 2 wks; NR	Grp1 B: 7 (SE: 0.1) F: 6.3 (SE: 0.1) p: <0.001 F-B: -0.7 Grp2 B: 7.1 (SE: 0.2) F: 6.5 (SE: 0.1) p: <0.001 F-B: -0.6 Grp1-Grp2: -0.1 (SE: 0.32) p: 0.146	Grp1 B: 92 (2) F: 92 (3) F-B: 0 Grp2 B: 91 (2) F: 94 (4) F-B: 3 Grp1-Grp2: -3 p: <0.001		
Wang, 2015[173]	Grp1: Metformin + placebo Fixed (>=1500 mg/day or maximum tolerated dose most patients (about 90%) had mean daily metformin dose >1500mg)	Grp1 B: NR F: -0.14 (NR) Grp2 B: NR	Grp1 B: NR F: -0.67 (2.64) Grp2 B: NR		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Grp2: Metformin + lingliptin Fixed (>=1500 mg/day or max tolerated dose most patients (about 90%) had >1500 mg/day dose) Fixed (5mg) ITT: NR Followup (wks): 24	F: -0.66 (NR)	F: -0.12 (2.83)		
Weissman, 2005[174]	Grp1: Metformin Varied Start: 1000 mg, Max: 2000 mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 1000 mg; Start: 4 mg, Max: 8 mg	Grp1 B: 7.97 (1.2) F: 7.26 F-B: -0.71 Grp2 B: 8.05 (1.2) F: 7.12 F-B: -0.93 Grp1-Grp2: 0.2			
White, 2014[175]	Grp1: Metformin + placebo Fixed (fixed dose metformin at >=1500 mg) Grp2: Metformin + saxagliptin Fixed (fixed dose but could be >=1500 mg) Fixed (5 mg) ITT: No Followup (wks):	Grp1: B: 7.97 (0.09) F: 7.75 (0.12) F-B: -0.22 (0.08) (-0.39-0.06) Grp2: B: 7.92 (0.11) F: 7.36 (0.13) F-B: -0.56 (0.09) (-0.74-0.38) Between-group difference: Grp2: -0.34 0.12 p 0.006	Grp1: F-B: -0.4 (-0.83-0.02) Grp2: F-B: -0.32 (-0.97-0.34)		
Williams-Herman, 2009[176]	Grp1: Metformin Fixed Mean: 2000 mg Grp2: Sitagliptin Fixed Mean: 100 mg	Grp1 F-B: -1.3 (CI: -1.5, -1.2) Grp2 F-B: -0.8 (CI: -1, -0.6) Grp1-Grp2: -0.5	Grp1 F-B: -1.5 (CI: -2.2, -0.8) Grp2 F-B: 0.6 (CI: -0.2, 1.4)		
Williams-Herman,	Grp1: Metformin Fixed	Grp1 F-B: -1 (CI: -1.2,	Grp1 F-B: -1 (CI:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
2009[176]	Mean: 1000 mg Grp2: Sitagliptin Fixed Mean: 100 mg	-0.8) Grp2 F-B: -0.8 (CI: -1, -0.6) Grp1-Grp2: -0.2	-1.7, -0.3) Grp2 F-B: 0.6 (CI: -0.2, 1.4)		
Williams-Herman, 2009[176]	Grp1: Metformin Fixed Mean: 2000 mg Grp2: Metformin + sitagliptin Fixed Mean: 2000 mg; Mean: 100 mg	Grp1 F-B: -1.3 (CI: -1.5, -1.2) Grp2 F-B: -1.8 (CI: -2, -1.7) Grp1-Grp2: 0.5	Grp1 F-B: -1.5 (CI: -2.2, -0.8) Grp2 F-B: -1.7 (CI: -2.4, -1.1)		
Williams-Herman, 2009[176]	Grp1: Metformin Fixed Mean: 2000 mg Grp2: Metformin + sitagliptin Fixed Mean: 1000 mg; Mean: 100 mg	Grp1 F-B: -1.3 (CI: -1.5, -1.2) Grp2 F-B: -1.4 (CI: -1.6, -1.3) Grp1-Grp2: 0.1	Grp1 F-B: -1.5 (CI: -2.2, -0.8) Grp2 F-B: -0.7 (CI: -1, 0) Grp1-Grp2: -0.8		
Williams-Herman, 2009[176]	Grp1: Metformin Fixed Mean: 1000 mg Grp2: Metformin + sitagliptin Fixed Mean: 2000 mg; Mean: 100 mg	Grp1 F-B: -1 (CI: -1.2, -0.8) Grp2 F-B: -1.8 (CI: -2, -1.7) Grp1-Grp2: 0.8	Grp1 F-B: -1 (CI: -1.7, -0.3) Grp2 F-B: -1.7 (CI: -2.4, -1.1) Grp1-Grp2: 0.7		
Williams-Herman, 2009[176]	Grp1: Metformin Fixed Mean: 1000 mg Grp2: Metformin + sitagliptin Fixed Mean: 1000 mg; Mean: 100 mg	Grp1 F-B: -1 (CI: -1.2, -0.8) Grp2 F-B: -1.4 (CI: -1.6, -1.3) Grp1-Grp2: 0.4	Grp1 F-B: -1 (CI: -1.7, -0.3) Grp2 F-B: -0.7 (CI: -1, 0) Grp1-Grp2: -0.3		
Williams-Herman, 2010[177]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No	Grp1: F-B:p Grp2: B: 8.6 (1) F: 8.6 (1) F-B: -1.7 (-1.8-1.5)	Grp1: F-B:p Grp2: F-B: -1.2 (-2--0.3)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Followup (wks): 104				
Williams-Herman, 2010[177]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: F-B:p Grp2: B: 8.7 (0.9) F: 8.7 (0.9) p F-B: -1.4 (-1.6-1.2) p	Grp1: F-B:p Grp2: F-B: 0.5 (-0.7-1.7) p		
Williams-Herman, 2010[177]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: F-B:p Grp2: B: 8.5 (0.9) F: 7.4 (0.7) F-B: -1.2 (-1.4-0.9)	Grp1: F-B:p Grp2: F-B: 0 (-0.8-0.9)		
Williams-Herman, 2010[177]	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.6 (0.9) F: 7.5 (0.7) F-B: -1.1 (-1.3-0.9) Grp2: B: 8.6 (1) F: 8.6 (1) F-B: -1.7 (-1.8-1.5)	Grp1: F-B: -0.8 (-1.9-0.3) Grp2: F-B: 0.5 (-0.7-1.7)		
Williams-Herman, 2010[177]	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.6 (0.9) F: 7.5 (0.7) F-B: -1.1 (-1.3-0.9) Grp2: B: 8.5 (0.9) F: 7.4 (0.7) F-B: -1.2 (-1.4-0.9)	Grp1: F-B: -0.8 (-1.9-0.3) Grp2: F-B: 0 (-0.8-0.9) p		
Williams-Herman, 2010[177]	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.6 (0.9) F: 7.5 (0.7) F-B: -1.1 (-1.3-0.9) Grp2: B: 8.7 (0.9) F: 8.7 (0.9) F-B: -1.4 (-1.6-1.2)	Grp1: F-B: -0.8 (-1.9-0.3) Grp2: F-B: -1.2 (-2--0.3)		
Williams-	Grp1: Metformin + placebo	Grp1:	Grp1:		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Herman, 2010[177]	Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	B: 8.5 (0.8) F: 7.2 (0.9) F-B: -1.3 (-1.5-1.2) Grp2: B: 8.6 (1) F: 8.6 (1) F-B: -1.7 (-1.8-1.5)	F-B: -2.4 (-3.3--1.5) Grp2: F-B: -1.2 (-2--0.3)		
Williams-Herman, 2010[177]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.5 (0.8) F: 7.2 (0.9) p F-B: -1.3 (-1.5-1.2) p Grp2: B: 8.5 (0.9) F: 7.4 (0.7) p F-B: -1.2 (-1.4-0.9) p	Grp1: F-B: -2.4 (-3.3--1.5) p Grp2: F-B: 0.5 (-0.7-1.7) p		
Williams-Herman, 2010[177]	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.5 (0.8) F: 7.2 (0.9) p F-B: -1.3 (-1.5-1.2) p Grp2: B: 8.7 (0.9) F: 8.7 (0.9) p F-B: -1.4 (-1.6-1.2) p	Grp1: F-B: -2.4 (-3.3--1.5) p Grp2: F-B: 0 (-0.8-0.9) p		
Williams-Herman, 2010[177]	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.5 (0.9) F: 7.4 (0.7) p F-B: -1.2 (-1.4-0.9) p Grp2: B: 8.7 (0.9) F: 8.7 (0.9) p F-B: -1.4 (-1.6-1.2) p	Grp1: F-B: 0.5 (-0.7-1.7) p Grp2: F-B: -1.2 (-2--0.3) p		
Williams-Herman, 2010[177]	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 104	Grp1: B: 8.5 (0.9) F: 7.4 (0.7) p F-B: -1.2 (-1.4-0.9) p Grp2: B: 8.6 (1) F: 8.6 (1) p F-B: -1.7 (-1.8-1.5) p	Grp1: F-B: 0.5 (-0.7-1.7) p Grp2: F-B: 0 (-0.8-0.9) p		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Xu, 2015[178]	Grp1: Pioglitazone Titrated 45 mg/d Grp2: Exenatide Titrated 10 ug twice daily	Grp1: B: 8(0.1) F: NR Grp2: B: 8(0.1) F: NR	Grp1: B: 70.6(1.1) F: NR Grp2: B: 71.7(1.1) F: NR	Grp1: B: 125(1) F: NR Grp2: B: 126(1) F: NR	
Yamanouchi, 2005[179]	Grp1: Metformin Fixed Start: 750 mg Grp2: Pioglitazone Fixed Start: 30 mg for women and 45 mg for men	Grp1 B: 9.9 (0.7) F: 7.8 (1.0) F-B: -2.1 p: <0.005 Grp2 B: 10.2 (0.8) F: 7.9 (1.0) F-B: -2.3 p: <0.005 Grp1-Grp2: 0.2			
Yamanouchi, 2005[179]	Grp1: Metformin Fixed Start: 750 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 2 mg	Grp1 B: 9.9 (0.7) F: 7.8 (1.0) F-B: -2.1 p: <0.005 Grp2 B: 9.8 (0.7) F: 7.7 (0.9) F-B: -2.1 p: <0.005 Grp1-Grp2: 0			
Yamanouchi, 2005[179]	Grp1: Pioglitazone Fixed Start: 30 mg for women and 45 mg for men Grp2: Glimepiride Varied Start: 1.0 mg, Max: 2.0 mg	Grp1 B: 10.2 (0.8) F: 7.9 (1.0) F-B: -2.3 p: <0.005 Grp2 B: 9.8 (0.7) F: 7.7 (0.9) F-B: -2.1 p: <0.005 Grp1-Grp2: -0.2			
Yang, 2011[180]	Grp1: Metformin + placebo Fixed (Mean: 1606 mg/dcontd pre-study dose: 1500 - 3000 mg/d) Grp2: Metformin + saxagliptin Fixed (Mean: 1620 mg/dcontd on prestudy dose - 1500 - 3000 mg/d)	Grp1: B: 7.9 (0.8) F: 7.55 (0.8) F-B: -0.37 (0.107) Grp2: B: 7.9 (0.8)	Grp1: B: 68.9 (0.7) F: 67.8 (0.7) F-B: -0.97 (0.1) Grp2: B: 68.9 (0.8)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	Fixed (5 mg/d) ITT: No Followup (wks): 18	F: 7.1 (0.8) F-B: -0.78 (0.183)	F: 67.7 (0.7) F-B: -1.05 (0.1)		
Yang, 2011[181]	Grp1: Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2: Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.2 mg1.2 mg target, started at 0.6 mg/day) ITT: No Followup (wks): 16	Grp1: B: 8.5 (1.1) F-B: -1.39 (0.11) (-1.5-) Grp2: B: 8.6 (1.1) F-B: -1.36 (0.14) (-1.5-) Between-group difference: Grp2: 0.03 (-0.14-0.2) p non-inferior	Grp1: B: 68.2 (11.9) F-B: 0.08 (0.26) Grp2: B: 68.6 (11.6) F-B: -1.8 (0.18) Between-group difference: p <0.0001	Grp1: B: 126 (14.9) F-B: -0.91 Grp2: B: 126 (14.3) F-B:	
Yang, 2011[181]	Grp1: Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2: Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.8 mg/dtarget 18 mg; started at 0.6 mg and up-titrated) ITT: No Followup (wks): 16	Grp1: B: 8.5 (1.1) F-B: -1.39 (0.11) (-1.5-) Grp2: B: 8.6 (1.1) F-B: -1.45 (0.15) (-1.6-) Between-group difference: Grp2: -0.06 (-0.23-0.11) p non-inferior	Grp1: B: 68.2 (11.9) F-B: 0.08 (0.26) Grp2: B: 67.4 (11.3) F-B: -2.35 (0.14) Between-group difference: p <0.0001	Grp1: B: 126 (14.9) F-B: -0.91 Grp2: B: 126 (14.1) F-B:p Between-group difference: p <0.05	
Yang, 2011[181]	Grp1: Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1	Grp1: B: 8.5 (1.1) F-B: -1.39 (0.11) (-1.5-) Grp2: B: 8.5 (1.1)	Grp1: B: 68.2 (11.9) F-B: 0.08 (0.26) Grp2: B: 68.2 (11.9) F-B: -2.44 (0.14)		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	mg and titrated over 2 weks) Grp2: Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Fixed (0.6mg daily) ITT: No Followup (wks): 16	F-B: -1.14 (0.16) (-1.3-)	Between-group difference: p <0.0001		
Yang, 2012[182]	Grp1: Metformin + placebo Fixed (1000 or 1700 mg/d) Grp2: Metformin + sitagliptin Fixed (1000 or 1700 mg/d) Fixed (100 mg/d) ITT: No Followup (wks): 24	Grp1: B: 8.6 (0.9) F-B: -0.1 (-0.3-0) Grp2: B: 8.5 (0.9) F-B: -1 (-1.2-0.9) Between-group difference: Grp2: 0.9 (-1.1-0.7) p<0.001	Grp1: B: 68.9 (13.3) F-B: -0.5 (-0.9--0.1) p Grp2: B: 67.9 (10.7) F-B: 0 (-0.3-0.4) p Between-group difference: Grp2: 0.5 (0.1-0.9) p 0.018	Grp1: B: 126 (14.9) F-B: -0.91 Grp2: B: 127 (14) F-B:p Between-group difference: p <0.05	
Yoon, 2011[183]	Grp1: Metformin Titrated (Mean: 1234.2 mgMax: 2000 mg/dstarted at 500 mg/d and titrated) Grp2: Rosiglitazone Titrated (Mean: 5.9 mgMax: 8 mg/dstarted at 4 mg in am) ITT: Yes Followup (wks): 48	Grp1: B: 7.9 (0.8) F: 7 p F-B: -0.92 (0.96) p <0.001 Grp2: B: 7.8 (0.8) F: 7 p0.62 F-B: -0.82 (0.79) p <0.001	Grp1: B: 68.9 (11.1) F: 69.9 (0.95) F-B: -1.1 Grp2: B: 67.9 (10.9) F: 71.2 (0.99) F-B: 1.4		
Yoon, 2011[183]	Grp1: Metformin Titrated (Mean: 1234.2 mgMax: 2000 mg/dstarted at 500 mg/d and titrated) Grp2: Glimepiride Titrated (Mean: 4.5 mg/dMax: 8 mg/dstarted at 2 mg in am) ITT: Yes Followup (wks): 48	Grp1: B: 7.9 (0.8) F: 7 p F-B: -0.92 (0.96) p <0.001 Grp2: B: 7.8 (0.8) F: 6.9 F-B: -0.89 (0.76) p 0.001	Grp1: B: 68.9 (11.1) F: 69.9 (0.95) p F-B: -1.1 p Grp2: B: 69.1 (12.1) F: 73.1 (1.36) F-B: 1.5		

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
Yoon, 2011[183]	Grp1: Rosiglitazone Titrated (Mean: 5.9 mgMax: 8 mg/dstarted at 4 mg in am) Grp2: Glimepiride Titrated (Mean: 4.5 mg/dMax: 8 mg/dstarted at 2 mg in am) ITT: Yes Followup (wks): 48	Grp1: B: 7.8 (0.8) F: 7 p0.62 F-B: -0.82 (0.79) p <0.001 Grp2: B: 7.8 (0.8) F: 6.9 p F-B: -0.89 (0.76) p 0.001	Grp1: B: 69.1 (12.1) F: 73.1 (1.36) F-B: 1.5 Grp2: B: 67.9 (10.9) F: 71.2 (0.99) F-B: 1.4		
Yuan, 2012[184]	Grp1: Metformin Titrated (started at 1000mg for 4 wks, 1500mg for 4-12 wks; if FPG>5.1mmol/l at week 12, met was increased to 2000mg; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be de Grp2: Exenatide Titrated (started at 10ug for 4 wks, 20ug for 4-12 wks without hypoglycemia; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be decreased 50% (additional episodes allowed ITT: Yes Followup (wks): 26	Grp1: B: 8.11 (1.92) F-B: -1.66 (1.38) p<0.001 Grp2: B: 8.27 (1.58) F-B: -2.1 (1.79) p<0.001 Between-group difference: p 0.045	Grp1: B: 83.7 (10.7) F-B: -3.81 (1.38) p<0.05 Grp2: B: 82.2 (12.8) F-B: -5.8 (1.66) p<0.05 Between-group difference: p <0.01		
Zhang, 2012[187]	Grp1: Metformin + glimepiride Fixed (1.0-1.5g, adjusted in accordance with the levels of blood glucose) Fixed (1-4mg, adjusted in accordance with the levels of blood glucose) Grp2: Metformin + exenatide Fixed (1.0-1.5g, adjusted in accordance	Grp1: B: 9 (0.9) F: 7.4 (0.6) F-B:p <0.01 Grp2: B: 8.7 (1) F: 7.4 (0.6)		Grp1: B: 139 (15) F: 137 (10) F-B:p >0.05 Grp2: B: 136 (13) F: 132 (9)	

Author, year	Intervention	Hemoglobin A1c, mean (SD)	Weight, mean (SD)	SBP, mean (SD)	Heart rate, mean (SD)
	with the levels of blood glucose) Fixed (initiated at 10ug for the first 4 wks, 20ug in the subsequent 12 wks then went into 16 week treatment period) ITT: No Followup (wks): 16	F-B:p <0.01 Between-group difference: p 0.08		F-B:p <0.01 Between-group difference: p >0.1	

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not Reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table D4. Quality of studies evaluating effects of diabetes medications on intermediate outcomes

Author, year	Randomized	Randomization Scheme Described	Double-blind	Blinding Method Desribed	Dropout Described
Aaboe, 2010[1]	Yes	No	Yes	Not described	No
Ahren, 2014[2]	Yes	Not described	Yes	Yes	Yes
Alba, 2013[3]	Yes	Yes	Yes	Not described	Yes
Apovian, 2010[4]	Yes	Yes	Yes	Not described	Yes
Arechavaleta, 2011[5]	Yes	Yes	Yes	Not described	Yes
Arjona Ferreira, 2013[6]	Yes	Yes	Yes	Yes	Yes
Aschner, 2012[8]	Yes	Yes	No	Not described	Yes
Bailey, 2013[10]	Yes	Yes	Yes	Yes	Yes
Barnett, 2012[13]	Yes	Yes	Yes	Yes	Yes
Bergenstal, 2010[14]	Yes	Yes	Yes	Yes	Yes
Bergenstal, 2012[15]	Yes	Yes	Yes	Yes	Yes
Bolinder, 2012[17]	Yes	Yes	Yes	Yes	Yes
Borges, 2011[18]	Yes	Not described	Yes	Not described	No
Cefalu, 2013[20]	Yes	Yes	Yes	Yes	Yes
Chawla, 2013[23]	Yes	Yes	NR/Can't tell	Not described	Yes
DeFronzo, 2005[28]	Yes	Yes	Yes	Yes	Yes
DeFronzo, 2012[31]	Yes	Not described	Yes	Yes	No
Del Prato, 2015[32]	Yes	Not described	Yes	Not described	No
Del Prato, 2014[33]	Yes	Not described	Yes	Yes	Yes
Derosa, 2011[40]	Yes	Yes	No	Not described	Yes
Derosa, 2013[42]	Yes	Yes	Yes	Yes	Yes
Derosa, 2013[43]	Yes	Yes	Yes	Yes	Yes
Diamant, 2010[44]	Yes	Yes	No	Not described	Yes
Erem, 2014[47]	Yes	Not described	No	Not described	No
Esposito, 2011[48]	Yes	Yes	Yes	Yes	Yes
Esteghamati, 2014[49]	Yes	Yes	No	Not described	No
Esteghamati, 2015[50]	Yes	Yes	No	No	Yes
Ferrannini, 2013[53]	Yes	No	No	Not described	No
Fidan, 2011[54]	Yes	Not described	No	Not described	No
Fonseca, 2012[56]	Yes	Yes	Yes	Not described	Yes

Author, year	Randomized	Randomization Scheme Described	Double-blind	Blinding Method Desribed	Dropout Described
Forst, 2010[57]	Yes	Yes	Yes	Yes	Yes
Forst, 2012[58]	Yes	Not described	No	Not described	Yes
Forst, 2014[59]	Yes	Not described	No	Not described	Yes
Gallwitz, 2011[60]	Yes	Not described	No	Not described	No
Gallwitz, 2012[61]	Yes	Yes	Yes	Yes	Yes
Gallwitz, 2012[62]	Yes	Yes	NR/Can't tell	Not described	Yes
Garber, 2011[67]	Yes	Yes	No	Not described	Yes
Genovese, 2013[68]	Yes	Not described	Yes	Yes	Yes
Genovese, 2013[69]	Yes	Yes	Yes	Yes	Yes
Goke, 2010[70]	Yes	Yes	Yes	Yes	Yes
Gupta, 2010[75]	Yes	Not described	No	Not described	No
Gupta, 2013[76]	Yes	Yes	No	Not described	Yes
Haak, 2012[77]	Yes	Not described	Yes	Not described	Yes
Haak, 2013[78]	Yes	Yes	Yes	Yes	Yes
Haring, 2014[83]	Yes	Yes	Yes	Yes	Yes
Henry, 2012[84]	Yes	Yes	Yes	Not described	No
Henry, 2012[84]	Yes	Yes	Yes	Not described	Yes
Hermans, 2012[87]	Yes	Not described	Yes	Not described	Yes
Ji, 2015[93]	Yes	Not described	Yes	Not described	Yes
Kadoglou, 2011[95]	Yes	Not described	No	Not described	Yes
Kadowaki, 2013[96]	Yes	Yes	Yes	Yes	Yes
Kaku, 2011[99]	Yes	Not described	No	Not described	
Kim, 2014[103]	Yes	Not described	No	Not described	Yes
Lavalle-Gonzalez, 2013[106]	Yes	Yes	Yes	Yes	Yes
List, 2009[109]	Yes	Yes	Yes	Yes	Yes
Maffioli, 2013[111]	Yes	Yes	Yes	Yes	Yes
Moon, 2014[114]	Yes	Not described	No	Not described	Yes
Nauck, 2009[119]	Yes	Yes	Yes	Not described	Yes
Nauck, 2011[120]	Yes	Yes	Yes	Yes	Yes
Nauck, 2014[121]	Yes	Not described	Yes	Not described	Yes
Petrica, 2009[126]	Yes	Not described	No	Not described	Yes

Author, year	Randomized	Randomization Scheme Described	Double-blind	Blinding Method Desribed	Dropout Described
Pfutzner, 2011[128]	Yes	Not described	Yes	Not described	No
Pfutzner, 2011[129]	Yes	Yes	Yes	Not described	Yes
Pratley, 2014[131]	Yes	Not described	Yes	Not described	Yes
Qiu, 2014[132]	Yes	Yes	Yes	Not described	Yes
Reasner, 2011[135]	Yes	Not described	Yes	Not described	Yes
Ridderstrale, 2014[136]	Yes	Yes	Yes	Yes	Yes
Roden, 2013[139]	Yes	Yes	Yes	Yes	Yes
Rosenstock, 2010[141]	Yes	Not described	Yes	Yes	Yes
Rosenstock, 2012[142]	Yes	Not described	Yes	Not described	Yes
Rosenstock, 2013[144]	Yes	Yes	Yes	Yes	Yes
Rosenstock, 2015[145]	Yes	Yes	Yes	Yes	Yes
Ross, 2012[146]	Yes	Yes	Yes	Yes	Yes
Russell-Jones, 2012[147]	Yes	Yes	Yes	Yes	Yes
Schernthaner, 2015[148]	Yes	Yes	Yes	Not described	Yes
Schondorf, 2011[150]	Yes	Not described	Yes	Not described	Yes
Schumm-Draeger, 2015[151]	Yes	Yes	Yes	Yes	Yes
Seino, 2012[156]	Yes	Yes	Yes	Yes	Yes
Shihara, 2011[157]	Yes	Yes	No	Not described	Yes
Suzuki, 2014[161]	Yes	Not described	No	No	No
Taskinen, 2011[164]	Yes	Not described	Yes	Not described	Yes
Taslimi, 2013[165]	Yes	Not described	NR/Can't tell	Not described	Yes
Umpierrez, 2014[171]	Yes	Yes	Yes	Yes	Yes
Wang, 2015[173]	Yes	Yes	Yes	Yes	Yes
White, 2014[175]	Yes	Yes	Yes	Yes	Yes
Williams-Herman, 2010[177]	Yes	Yes	Yes	Yes	Yes
Xu, 2015[178]	Yes	Not described	No	No	No
Yang, 2011[180]	Yes	Yes	Yes	Not described	Yes
Yang, 2011[181]	Yes	Not described	Yes	Yes	Yes
Yang, 2012[182]	Yes	Yes	Yes	Yes	Yes
Yoon, 2011[183]	Yes	Not described	Yes	Not described	Yes
Yuan, 2012[184]	Yes	Yes	No	Not described	Yes

Author, year	Randomized	Randomization Scheme Described	Double-blind	Blinding Method Desribed	Dropout Described
Zhang, 2012[187]	Yes	Not described	No	Not described	Yes

Table D5. Characteristics of studies evaluating effects of diabetes medications on long-term outcomes

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Agarwal, 2005 [189] US Not extracted	RCT	Start year: 2001 End year: 2003 16 Wks	No run-in period	Yes	102/54 Outpatient: subspecialty care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI >40 kg/m^2, class III or IV heart failure, NSAID use
Ahren, 2014[2] Country NR NCT00838903	RCT	2009 2013 104 wks	Yes	Yes	NR/1049 NR	Adequate glycemic control while taking background metformin (>=1500mg or maximum tolerated dose) >=3 months before screening. Any liver disease. Any kidney disease. Abnormal thyroid-stimulating hormone concentration and not clinically euthyroid. Ongoing symptomatic biliary disease. History of pancreatitis. Recent clinically significant cardiovascular and/or cerebrovascular disease (<=2 months before screening). Treated gastroparesis. History of GI surgery thought to significantly affect upper GI function. History of most cancers not in remission for at least 3 years. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. Resting systolic blood pressure (SBP)>160mmHg and/or diastolic blood pressure(DBP)>100mmHg. Additional exclusion criteria: hemoglobinopathy that could affect HbA1c,lipase> ULN. "any liver disease": ALT or AST more than 2.5 times the ULN."any kidney disease": creatinine clearance <=60ml/min using the Cockcroft-Gault formula. withdrawal criteria: loss to follow-up, protocol violation, noncompliance, withdrawal of consent, Also stated that did race subgroup analysis in methods but not reported in results. withdrawal criteria: an AE/lab result requiring withdrawal (QTc prolongation, elevation of liver function test results, severe potential allergic reactions, confirmed pancreatitis, severe or repeated hypoglycemia, calcitonin>100pg/ml).

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Alba, 2013[3] Multi-continent NCT00511108	RCT	Neither year reported 12	Yes	Yes	Not Extracted/ 211 NR	Age <30 or >65 yrs, HbA1c >10% if drug naive, 9% if on antihyperglycaemic agent monotherapy or low-dose combination therapy or <7% if drug naive, 6.5% if on antihyperglycaemic agent monotherapy or low-dose combination therapy, Any liver disease, Any kidney disease, History of CVD, current use of sitagliptin, vildagliptin, exenatide, PPARr agonist within the prior 12 wks fasting fingerstick glucose <7.2mmol/l or 14.4mmol/l at week -2
Amador-Licona, 2000[186] Mexico Not extracted	RCT	12 wks (planned duration)	Not extracted	No	Not extracted	Age >65 years, any liver disease, history of CVD, other
Andersson, 2010[190] Denmark No	Retrospective cohort	1997 2006 844 days	Not applicable	Yes	10,920 / 5,852 Administrative database, The Danish National Patient Register - The Danish Register of Medicinal Product Statistics and The National Causes of Death Register Inpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <= 30 yrs, No diagnosis/hospitalization for CHF, not using MET, SU and/or Insulin, Use of other glucose lowering meds, patients with previous hospitalisations for HF during the period from 1978 until 1996 (diagnosis codes [ICD-10] I50, I42, J81, I11.0 and [ICD-8] 425, 4270, 4271) were excluded from the study, not alive 30 days after discharge for CHF, not receiving drug of interest 30 days after discharge for CHF, use of study drug within 90 days of hospitalization fro CHF
Arechavaleta, 2011[5] multi-national NCT00701090	RCT	Neither year reported 30	Yes	Yes	Not Extracted/ 1035 NR	Age <18 years, HbA1c >9% or <6.50%, Not on a stable dose of metformin (ГёÑ1500 mg/day) as well as diet and exercise for past 12 wks, history of type 1 diabetes, used any Anti Hypoglycemic Agent besides metformin within 12 wks of the screening visit, renal function impairment prohibiting the use of metformin, fasting fingerstick glucose of <6.1 or >13.3 mmol/l at randomization, stable meds for HTN, thyroid dz, HRT, OCPs

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Arjona Ferreira, 2013[6] Multinational NCT00509262	RCT	Neither year reported 58	Yes	Yes	Not Extracted/ 426 NR	Age <30 yrs, HbA1c >9.00% or <7.00%, Prior or current use of insulin, Any liver disease, did NOT have moderate to severe chronic renal insufficiency (eGFR>=50 ml/min/1.73m2 using the Modification of Diet in Renal Disease equation), on dialysis or likely to require dialysis for the duratoin of the study, acute renal disease, history of renal transplant, history of ketoacidosis, recent (within 3 months) cardiovascular event, thyroid stimulating hormone outside the reference range, triglycerides>600mg/dl, visit2, FPG>260mg/dl, unlikely to improve with diet/exercise, visite 3, FPG>250mg/dl consistently (i.e., measure=ment repeated and confirmed within 7 days); visite 4, FPG>240mg/dl consistently visit5, finger-stick glucose > 240 or <120mg/dl
Aschner, 2010[7] Multi-continent Not extracted	RCT	Neither year reported 24 wks	Run-in period but number of participants excluded NR	Yes	2068/1050 NR	Age <18 or >78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >9%, treatment naive, no Type 2 DM, FPG <120 or >250 mg/dL, triglycerides >600 mg/dL, CK > 2x upper limit normal
Aschner, 2012[8] Multi-continent NCT00751114	RCT	2008 2011 24	No	Yes	Not Extracted/ 515 NR	Age <35 - >70 yrs, HbA1c >=11% or <7%, BMI <25 - >45, Any liver disease, Any kidney disease, FPG >14.4 mmol/L, tx'd w/ oral other than metformin in past 3 mo, received SU+MET In past year prior use of GLP-1 or DPP-4, any disorder that the investigator felt woudl compromise the patient's safety, unwilling to self-monitor BG or keep diary
Bailey, 2005[9] UK, 14 European countries Not extracted	RCT	24 wks (planned duration)	Not extracted	Yes	Not extracted	Age <18 or >70 years, history of CVD, no Type 2 DM, other

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Bailey, 2013[10] Multi-continent NCT00528879	RCT	2007 2008 102	Yes	Yes	Not Extracted/ 546 NR	Age <18 and >77 yrs, HbA1c >10% or 7%, BMI >45 kg/m^2, Any liver disease, Any kidney disease, History of CVD, C-peptide concentration <0.34 nmol/L, not taking stable dose of metformin for at least 8 wks prior to enrollment, creatine kinase more than 3 times upper limit of normal, symptoms of poorly controlled diabetes, systolic blood pressure >=180 mmHG, diastolic blood pressure >=110 mmHG, clinically significant haematological, oncological, endocrine, psychiatric, or rheumatic disease, New York Heart Association class III or IV congestive heart failure
Bakris, 2003[11] likely US and UK Not extracted	RCT	52 wks (planned duration)	Not extracted	Yes	Not extracted	NR
Bakris, 2006[12] US, Multi-continent, South America, Europe Not extracted	RCT	Neither year reported 32 Wks	Yes	Yes	560/514 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI < 22 kg/m^2, use of any TZD in the 3 months prior to screening, use of insulin for ≥6 months at any time prior to screening, anemia, severe angina, SBP >159 mm Hg (can't adjust the BP meds during the trial), DBP >99 mm Hg
Barnett, 2012[13] Multi-continent NCT00740051	RCT	2008 2010 52	Yes	Yes	Not Extracted/ 227 NR	Age <18 or >80 yr, HbA1c: If treatment naive: L10.0%(9.0% for Canada); If receiving an oral antidiabetes drug: 9.0%, HbA1c: If treatment naive: <7.0%; If receiving an oral antidiabetes drug: 6.5%, BMI >40kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, MI, stokre, or TIA in last 6 months, changed glucose-lowing treatment <10 wks prior to informed consent, hereditary galactose intolerance, treatment with GLP-1 analogue, TZD, or an antiobesity drug within the previous 3 months, or any investigational agent within the previous 2 months, hypersensitivity or allergy to the investigational drugs

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Bergenstal, 2010[14] Multi-continent NCT00637273	RCT	2008 2008 26	No	Yes	Not Extracted/ 514 Outpatient: primary care	Age <18years, HbA1c >11% or <7.10%, BMI <25 and greater than 45kg/m2, Prior or current use of insulin, Prior or current use of study drug, Pregnant, Nursing, Not using adequate contraception, not treated with a stable metformin regimen for at least 2 months before screening, no type 2 diabetes, fasting plasma glucose >/= 280 mg/dL (15.5 mmol/L), clinically significant laboratory test values, physical examination, or electrocardiogram results, clinically significant medical condition (e.g., hepatic disease, renal disease, cardiovascular disease, gastroparesis, malignant disease, macular edema, chronic infections), drug or alcohol abuse, donated blood within 60 days of screening or planning to donate blood during study, major surgery or blood transfusion within 2 months of screening, current treatment with alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide, systemic corticosteroids or intrapulmonary steroids, drugs interacting with the CYP2C8 enzyme system, or any investigational drug, known allergies or hypersensitivity to any component of study treatment, or previously experienced a clinically significant adverse event related to TZD or DPP-4 inhibitor use

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Bolinder, 2012[17] Europe NCT00855166	RCT	2009 2011 102	Yes	Yes	Not Extracted/ 182 NR	Women age <55 or >75 years. Men <30 or >75 years, HbA1c >8.50% or <6.50%, BMI <25kg/m^2 and body weight >120 kg, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, Fasting plasma glucose >240 mg/dl (>13.2 mmol/liter), diabetes treatment includes other drugs besides metformin, metformin treatment <1500 mg/d, not on stable metformin treatment at least 12 wks before enrollment, perimenopausal women, body weight change >5% within 3 months, serum total bilirubin >34 ╬╠ mol/L; hemoglobin (Hb) Γëñ105 g/L (10.5 g/dL) for men and Γëñ95 g/L (9.5 g/dL) for women; abnormal thyroid stimulating hormone level; 25-hydroxyvitamin D level <12 ng/mL (<30 nmol/L), history of osteoporotic fracture, bilateral hip replacement, spinal deformity or spinal surgery, metabolic bone disease or disease known to significantly influence bone metabolism or use of medication known to significantly influence bone metabolism within 6 months of enrolment, T-score less than ΓêÆ2.0 for bone mineral density at lumbar spine, femoral neck, or total hip at baseline DXA measurement, systolic blood pressure ΓëÑ180 mmHg and/or diastolic blood pressure ΓëÑ110 mmHg; cardiovascular event within 6 months of enrolment; congestive heart failure significant respiratory, hematological, oncological, endocrine, immunological (including hypersensitivity to study medications) alcohol and/or substance misuse disorders; a history of bariatric surgery; use of weight loss medication within 30 days of enrolment
Borges, 2011[18] Multi-continent NCT00386100	RCT	2006 2008 80	No	Yes	Not Extracted/ 688 NR	Age <18 - >75 yrs, HbA1c >10.5% or <7.5%, BMI < =25 Prior use of any diabetes treatment fasting glucose <7 mmol/l

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Brownstein, 2010 [191] United States Not extracted	Cohort	Start year: 2000 End year: 2006 7 years	NA	No	NA/34252 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Age ≤18 years, HbA1c ≤ 6.0%, no diagnosis of DM with ICD-9 code of 250.XX
Cefalu, 2013[20] Multi-continent NCT00968812	RCT	2009 2011 52	Yes	Yes	Not Extracted/ 1452 NR	Age <18, >80 yrs, HbA1c >9.5 or <7%, Any kidney disease, Not on stable metformin therapy (ГёÑ2000 mg per day or ГёÑ1500 mg per day if unable to tolerate a higher dose) for at least 10 wks, prior TZD use in 16 wks before screening, h/o more than 1 severe hypoglycemic episode within 6 months, repeated measurements of fasting plasma glucose or fasting self-monitored blood glucose, or both, of 15–10 mmol/L or more during the pretreatment phase;
Comaschi, 2007[25] Italy Not extracted	RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	Yes	398/250 NR	Age <35 years, HbA1c <7.5% or >11%, had not received SU or metformin as a monotherapy at a stable dose for at least 3 months, fasting C-peptide <0.33 nmol/L
Corrao, 2011[192] Italy	Retrospective cohort	2001 2003 4.8-5.1	Not applicable	No	Not Extracted/ 70,437 Administrative database, health service databases of Lombardy, Inpatient diagnosis/procedure, Outpatient pharmacy records, database for regional National Health demographic and administrative data	Age <40, >90 yrs, Prior use of any diabetes treatment, Prior or current use of insulin, History of CVD, macrovascular disease hospitalization, resident of Lombardy region, < 1 year FU, started treatment on combination therapy of MET + SU, received fewer than 2 prescriptions for diabetes drugs during follow up

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
DeFronzo, 1995[27] US Not extracted	RCT	29 wks (planned duration)	Not extracted	No	Not extracted	Age <40 or >70 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
DeFronzo, 2012[31] Multi-continent NCT00328627	RCT	Neither year reported 26	Yes	Yes	Not Extracted/ 1554 NR	Age <18 or >80 yr, HbA1c >10% before and after run-in/stabilization period or <7.5% before and after run-in/stabilization period, BMI <23 or >45kg/m2, Any liver disease, Any kidney disease, Retinopathy, Not using adequate contraception, fasting C-peptide <0.26nmol/l, not on met monotherapy (stable met dose >1500mg/d for >=2 months), SBP/DBP>160/100mmHg, hemoglobin < 12g/dl for men, <10g/dl for women, class 3 or 4 CHF, cardiac surgery or acute MI within last 6 months, TSH > ULN, treated diabetic gastroparesis, no willingness or ability to perform self-monitoring of blood glucose or to provide written informed consent, FPG>16.7mmol/l after run-in/stabilization period, oral or systemically injected glucocorticoids or weight-loss drugs within 3 months of randomization
Del Prato, 2015[32] Multi-continent NCT00660907	RCT	Neither year reported 208 wks	No	Yes	NR/814 NR	NR
Del Prato, 2014[33] Mutli-continent NCT00856284	RCT	Neither year reported 104 wks	Yes	Yes	NR/2639 NR	Systolic blood pressure >150mm hg. Diastolic blood pressure >90 mm hg. History of cancer. Prior use of any other diabetes drug for the last 2 months.

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Diamant, 2010[44] Multi-continent NCT00641056	RCT	2008 2009 26	Yes	Yes	Not Extracted/ 321 NR	Age <18 years or older, HbA1c >11% or <7.1%, BMI <25kg/m2 and >45kg/m2. Unstable body weight within 3 months, more than three episodes of major hypoglycaemia within 6 months of screening, treatment within 4 wks of screening with systemic glucocorticoids, treatment for longer than 2 wks with insulin, thiazolidinediones, ╬-glucosidase inhibitors, meglitinides, exenatide twice-aday formulation, dipeptidyl peptidase-4 inhibitors, or pramlintide acetate within 3 months of screening, not treated with a stable dose of metformin of 1500 mg or more per day for at least 8 wks prior to screening
Ekstrom, 2012[193] Sweden	Retrospective cohort	2004 2010 3.9	Not applicable	No	Not Extracted/ 51675 Outpatient: primary care and subspecialty care setting, National Diabetes Register, prescribed drug register, the patient register and the cause of death register, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age >=85 or <45 yrs, not registered in Nat'l diabetes Register 1 yr prior to and 1 yr following first prescription of glucose-lowering tx, less then 3 prescriptions or less than 18 fills of mulidose dispensed drugs during 12 months of continuous use of glucose-lowering med

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Erem, 2014[47] Turkey Not Extracted	RCT	Neither year reported 52	Yes	No	Not Extracted/ 60 NR	Age <30 or >70 yr, HbA1c <8% when FPG<126mg/dl, <7% if FBG is 126 -139 mg/dl and HOMA-IR>3, not newly diagnosed, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, COPD, ketoacidosis or ketonuria NYHAC Class 3/4 CHF, history of lactic acidosis, malignancy, thyroid disease or chronic inflammatory diseases or rheumatic disease, substance abuse, steroid treatment, active infection
Esposito, 2011[48] Italy Not Extracted	RCT	Neither year reported 24	No	Yes	Not Extracted/ 110 investigators' practices	Age <30 and >75 years, HbA1c >10% or 7%, BMI </=25kg/m2 and unstable weight in last 6 months or evidence of participation in weight reduction programs, "Newly diagnosed", Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Pregnant, Nursing, any investigational drug in past 3 mo, use of agents affecting glycaemic control (such as systemic glucocorticoids and weight loss drugs), acute disease or infection, recent (within 3 months) cardiovascular events or surger, immunological disorders, any condition that might compromise adherence to the study, patients with positive antibodies to glutamate decarboxylase, participation in weight loss program or unstable wt in past 6 mo, patients with C-peptide levels less than 0.25 pmol/l (<0.76 ng/l)
Farcasiu, 2011[51] Multi-continent Not Extracted	RCT	2006 2009 16	Yes	Yes	Not Extracted/ 302 NR	Age <30 - >75 yrs, HbA1c >1.8 X ULN or <1.2 X ULN, BMI >40 kg/m2, Any liver disease, metformin <1500mg, on other oral dm med besides metformin, history of severe hypoglycemia within 6 months, CHF, renal transplantation, irregular sleep-wake cycle

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Ferrannini, 2013[194] Multi-continent NCT00789035	RCT	Neither year reported 12	Yes	Yes	Not Extracted/ 408 NR	Age, <18 or >79 years, HbA1c> 9% if on antidiabetic drug, >10 if tx naïve or <6.5 if on antidiabetic drug, <7 if treatment naïve, BMI >40 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, not treatment naive or on stable dose of more than one antidiabetic drug (except GLP1, insulin, TZDs) in past 10 wks, myocardial infarction, stroke or transient ischaemic attack Γëñ6 months prior, unstable or acute congestive heart failure, acute or chronic acidosis; disease of CNS, psychiatric d/o or clinically relevant neuro d/o, chronic or clinically relevant acute infection, current or chornic urogenital tract inf, dehydration, hereditary galactose intolerance, tx with antiobesity drugs, systemic steroids, alchol abuse, tx with investigational drug <=2 m prior, neurologic/psychiatric issues that might interfere with participation
Fonseca, 2000[55] US Not extracted	RCT	26 wks (planned duration)	Not extracted	No	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no Type 2 DM, other
Fonseca, 2012[56] US and Latin America NCT00960076	RCT	2009 2010 18	Yes	Yes	Not Extracted/ 282 NR	Adults, HbA1c >11% or <7.5%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Not using adequate contraception, weight loss >10% in 3 mo before screening, unable to finish lead-in period (stabilitized on met 1500 mg/d), history of ketoacidosis, alcohol or drug abuse or unstable psychiatric disorder, hemoglobinopathy, blood/plasma donation in past 3 mo, anemia or significant lab/ecg abnormalities, investigational drugs or partiipation in a clinical trial in last mo, treatment with any other diabetes med (besides met) in past 8 wk, tx with potent CYP 450 3A drug or contradind to / h/o tx w/ saxa

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Forst, 2010[57] Europe NCT00309608	RCT	Neither year reported 12	Yes	Yes	Not Extracted/ 333 NR	Age <21 or >75 yr, HbA1c>9.0% for patients previously treated with met and one other oral anti-diabetic drug; 10.0% for patients perviously treated with met alone; 10% for all patients after run-in phase or HbA1c >7.0% for patients previously treated with met and one other oral anti-diabetic drug; 7.5% for patients previously treated with met alone; 7.5% for all patients after run-in phase, BMI <25 or >40 kg/m2, Prior or current use of insulin, previously treated with therapy other than 1. met alone; 2. met and one other oral hypoglycaemic agent other than rosi or pio., anti-diabetic therapy changed within 10 wks prior to screening, FPG concentrations > 13.3mmol/l (measured on 2 separate days), treated with rosi or pio within 6 months prior to screening, one or more of a list of specified clinical lab abnormalities (not specified in article), clinically relevant stroke, MI, TIA within 6 months
Gallwitz, 2012[61] Multi-continent NCT00622284	RCT	2008 2010 104	Yes	Yes	Not Extracted/ 1552 Outpatient: primary care, Outpatient: subspecialty care setting	Age <18, >80 years, BMI >40 kg/m^2, Prior or current use of insulin, Any liver disease, History of CVD, Not on stable metformin dose >= 1500mg/day (alone or with another antidiabetic drug), HbA1c <6.5% or >10% if participant on metformin alone prior to enrollment, HbA1c <6% or >9% if participant on metformin and another anti-diabetic medication prior to enrollment, myocardial infarction, stroke, transient ischemic attack 6 months prior to screening, treatment with rosiglitazone, pioglitazone, GLP-1 analogue or agonist 3 months prior to screening, On anti-obesity drug in 3 months prior to screening
Gallwitz, 2012[62] Multi-continent NCT00359762, EudraCT 2005-005448-21	RCT	2006 2011 48	No	Yes	Not Extracted/ 1029 NR	Age <18 or >85 yrs, HbA1c >9% or <6.5%, BMI <25 or >=40 prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, adequate response to metformin based on HbA1c criteria, contraindication to glimepiride, active/untreated cancer or cancer in remission <5 yrs, hemoglobinopathy or significant anemia, severe GI disease, on drugs affecting motility, glucocorticoids, weight loss drugs in last 3 mo, treatment for more than 2 wks in past 3 mo with insulin, TZDs, alpha glucosidase inhib, SUs, meglitinides

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Garber, 2003[64] US Not extracted	RCT	16 wks (planned duration)	Not extracted	Yes	Not extracted	Age < 20 or >79 years, any liver disease, any kidney disease, treatment experienced, HbA1c >7% or <12%, no Type 2 DM, other
Garber, 2011[67] US Mexico NCTC00294723	RCT	2006 2008 104	No	Yes	Not Extracted/ 746 NR	Age <18 or >80, HbA1c >11% if on diet/exercise or >10% if on monotherapy or <7%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia
Genovese, 2013[68] Italy NCT00772174	RCT	Neither year reported 24	Yes	Yes	Not Extracted/ 213 NR	Age <35 or >75 yr, Any liver disease, Any kidney disease, Pregnant, Nursing, Not using adequate contraception, not taking metformin (2000-30000mg/day) for at least 3 months, HDL-C levels >=40mg/dl in males and >=50mg/dl in females irrespective of statin tx, anemia of any etiology (Hb<10.5g/dl) or any other hematological disease; diagnosis or suspicion of neoplastic disease, no central obesity (excluded if waist circumference <94 cm for men and <80 cm for women), using oral anti-diabetic drugs other than met or insulin in the 3 months preceding study entry, treatment with fibrates or rifampicin, acute or chronic pancreatitis or familial polyposis, history of chronic alcohol or drug/substance abuse, satisfactory drug compliance (compliance ranging between 80-120%) during run-in, medical history of MI, transient ischemic attacks or stroke in the past 6 months, designation of class 1-4 heart failure according to NYHA criteria

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Genovese, 2013[69] NR ACTRN1260800053 4381	RCT	Neither year reported 16	Yes	Yes	Not Extracted/ 58 Outpatient: subspecialty care setting	Age <35 or >75 yr, HbA1c >9.00%, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, lack of cooperative attitude and ability to be treained to use the investigational drugs correctly or to attain the study procedures, participation in another trial in the 3 months preceding study entry, any disease with malabsorption, or familial polyposis or pancreatitis, congestive heart failure (NYHA class 1-4), anemia of any etiology (hemoglobin level < 10.5g/dl) or any other clinically relevant hematologic disease, diagnosis or suspicion of any neoplastic disease, history of chronic alcohol or drug/substance abuse, or presence of other conditions potentially able to affect study stubjects compliance, concomitant therapy with statins, antioxidant drugs (e.g. vitamins, Q10 coenzyme), beta-blockers, nonsteroidal anti-inflammatory drugs, aspirin, corticosteroids,, known allergy, sensitivity, ,or intolerance to study drugs and/or study drugs' formulation ingredients (pioglitazone, met marked above)
Goke, 2010[70] Multi-continent NCT00575588	RCT	2007 2010 104	Yes	Yes	Not Extracted/ 858 NR	Age <18 years, HbA1c >10% or <6.50%, Prior or current use of insulin, Prior or current use of study drug, Any liver disease, Any kidney disease, no type 2 diabetes, not on stable metformin monotherapy >=1500mg/day for at least 8 wks prior to enrollment, type 1 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, donation of blood, plasma or platelets within the 3 months prior to enrolment, history of haemoglobinopathies; significant alcohol or drug abuse within the year prior to enrolment, treatment with human immunodeficiency virus Гüä antiviral drugs or cytochrome P450 3A4 (CYP450 3A4) inducers, treatment with a thiazolidinedione within 12 wks prior to enrollment, congestive heart failure, significant cardiovascular history within the past 6 months

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Goldstein, 2003[71] US Not extracted	RCT	18 wks (planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% or >12.0%, other
Gomez-Perez, 2002[73] Mexico Not extracted	RCT	26 wks (planned duration)	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Haak, 2012[77] Multi-continent NCT00798161	RCT	2008 2010 24	Yes	Yes	Not Extracted/ 791 NR	Age <18 or >80 years, HbA1c >10.5% if on OAD or >=11% if treatment naïve or <7.0% if on OAD or <7.5% if treatment naïve, BMI > 40 kg/m2, Prior or current use of insulin, Any kidney disease, History of CVD, Pregnant, Nursing, neither treatment naive nor had been treated with OAD monotherapy, prior treatment with rosiglitazone, pioglitazone, GLP-1 analogs, or anti-obesity drugs in the previous 3 months, receiving treatment with systemic steroids or had a change in dosage of thyroid hormones in the previous 6 wks, had undergone gastric bypass, Had known hypersensitivity or allergy to linagliptin or its excipients, metformin or placebo, had a history of alcohol or drug abuse in the previous 3 months, had acute or chronic metabolic acidosis, had hereditary galactose intolerance, had experienced a myocardial infarction, stroke, or transient ischemic attack in the previous 6 months
Haak, 2013[78] Multi-continent NCT00915772	RCT	2009 2011 52	Yes	Yes	Not Extracted/ 567 NR	Pregnant, Nursing, Not using adequate contraception, completed the previous 6-month trial, were not on rescue medication, alcohol abuse within the past 3 months or drug abuse that would have interfered with trial participation
Hallsten, 2002[79] Finland Not extracted	RCT	26 wks (planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Hamann, 2008[80] Multinational Europe, Mexico Not extracted	RCT	Neither year reported 52 Wks	Yes	NR	818/596 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >10%, BMI <25 kg/m^2, used any ODM other than metformin in the prior 12 wks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin < 11.0 g/dl for men and < 10.0 g/dl for women), C-peptide <0.5nmol/L, SBP >170 mmHg, DBP >100 mmHg
Hanefeld, 2004[81] Canada, UK, Hungary, Finland, Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and Netherlands Not extracted	RCT	NR	Not extracted	Yes	Not extracted	Age <35 or >75 years, history of CVD, HbA1c <7.5% or >11%, no Type 2 DM, other
Hanefeld, 2007[82] Multinational Europe Not extracted	RCT	Neither year reported 52 Wks	Run-in period but number of participants excluded was NR	Yes	NR/598 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI <22 kg/m^2 or >38 kg/m^2, pregnant, patient on insulin therapy, patient with diabetic complications requiring treatment, hematologic impairment, FPG: <7 mmol/l or >15 mmol/l, C-peptide <0.27 nmol/l

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Haring, 2014[83] Multi-continent NCT01159600	RCT	2010 2012 24	Yes	Yes	Not Extracted/ 638 NR	Age <18 yrs, HbA1c >10% or <7%, BMI >45 kg/m2, Any liver disease, Contraindication or history of intolerance to metformin, not on stable MFM IR unchanged >=12 wks prior to randomization, uncontrolled hyperglycemia (glu> 13.3mmol/L) after overnight fast confirmed by 2nd measurement, ACS, stroke, TIA within 3 mo, bariatric surgery or other GI surgeries that induce chronic malabsorption, cancer (except basal cell ca) or tx for CA within last 5 yrs, blood dyscrasias, hemolysis, unstable erythrocytes, tx with antiobesity drugs 3m prior, use of tx leading to unstable body weight, tx with systemic steroids, change in dose of thyroid hormones within 6w, alcohol or drug abuse within 3m, investigational drug in another trial with 30d, eGFR<30
Henry, 2012[84] Multi-continent NCT00643851	RCT	2008 2009 24	Yes	Yes	Not Extracted/ 603 Inpatient/hospital Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 or >77, HbA1c >12 or <7.5, BMI >45, Any liver disease, Any kidney disease, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), New York Heart Association Class III or IV congestive heart failure, systolic blood pressure ΓÇí 180 or diastolic blood pressure ΓÇí 110 mmHg., a cardiovascular event within 6 months, other significant renal, hepatic, hematologic, oncologic, endocrine, psychiatric, or rheumatic disease
Henry, 2012[84] Multi-continent NCT00859898	RCT	2009 2010 24	Yes	Yes	Not Extracted/ 641 Inpatient/hospital Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 or >77 yrs, HbA1c >12% or <7.5%, BMI >45 kg/m2, Any liver disease, Any kidney disease, History of CVD, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), New York Heart Association Class III or IV congestive heart failure, systolic blood pressure ΓÇí 180 or diastolic blood pressure ΓÇí 110 mmHg., a cardiovascular event within 6 months
Hermann, 1994[86] Sweden Not extracted	RCT	6 months (planned duration)	Not extracted	Yes	Not extracted	No Type 2 DM, other

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Hermans, 2012[87] Europe NCT01006590	RCT	Neither year reported 24	Yes	Yes	Not Extracted/ 286 NR	Age <18 yrs, HbA1c >10, HbA1c <7, Prior or current use of insulin, Contraindication or history of intolerance to metformin, Pregnant, Nursing, type 1 DM, history of DKA or HONC, prior use of injectable GLP-1 analogues within 3mo of study, treatment with systemic glu- cocorticoids other than replacement therapy (inhaled, local injected and topical use of glucocorticoids were allowed), treatment with cytochrome P450 3A4 inducers, not on stable tx with metfomrin 1500-1700 mg/d
Home, 2009[89] Multinational Europe Not extracted	RCT	Start year: 2001 End year: 2003 7.5 Years	Run-in period but number of participants excluded was NR	Yes	7428/4458 Outpatient: primary care	Age <40 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), contraindication or history of intolerance to metformin, HbA1c < 7% or >9%, BMI <25 kg/m^2, pregnant, nursing, not using adequate contraception, recent CAD event, heart failure
Hong, 2013[195] China NCT00513630	RCT	2004 2007 36	Yes	Yes	Not Extracted/ 304 clinical centers	Age >80yr, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, not diagnosed as CAD (either having a history of acute myocardial infarction diagnosed by a representative set of electrocardiograms, cardiac enzyme values, and typical symptoms or by angiographically identified stenosis of >50% of lumen diameter in at le, severe dysfunction of the heart (NYHA class > phase 3), other severe organic heart diseases, including but not limited to congenital heart disease, rheumatic heart disease, hypertrophic or dilated cardiomyopathy; psychiatric disease, severe infection, severe anemia, Neutropenia, allergic to study drugs, fasting plasma glucose>=15 mmol/l, recent drug or alcohol abuse

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Horsdal, 2011[196] Denmark Not Extracted	Case-control	1996 2004 6	No	Yes	Not Extracted/ 101313 Administrative database, Danish National Patient Registry, Registry of Medicinal Product Statistics, National Health Insurance Service Registry, Inpatient diagnosis/ procedures, Outpatient diagnosis/ procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <30, controls matched up to 10:1 to the cases based on age and gender
Hsiao, 2009[197] Taiwan Not extracted	Cohort	Start year: 2000 End year: 2005 6 years	NA	NR	NA/20450 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Type 1 DM, prescribed insulin only during study period, new diagnosis of Type 2 DM during the year before index date, switch between rosiglitazone and pioglitazone or combined use of both drugs during study period, prescribed ODM less than three times during study period

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Hung, 2012[198] US Not extracted	Retrospective cohort	2001 2008 0.7-0.9	Not applicable	No	Not Extracted/ 93577 Inpatient/hospital Outpatient: primary care, Outpatient: subspecialty care setting, VA health system, VA health system, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <18, Any liver disease, Any kidney disease, less than 365 days of active use of VHA pharmacy services with diabetes drug filled, unknown birthdate, gender, race, less than 365 days of baseline data, missing eGFR, missing creatinine, CHF, HIV/AIDS, cancer except non-melanoma skin ca, transplant, cocaine use, baseline Cr>1.5, eGFR<60, combo therapy
Hung, 2013[199] Taiwan Not extracted	Retrospective cohort	1998 2007 3.1-3.8	Not applicable	No	Not Extracted/ 1159 Administrative database, Taiwan National Health Insurance Research Database, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures	Age <30 yrs, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, cancer, followup <0.5 yr, Use of concomitant DM2 medications

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Hung, 2013[200] US Not extracted	Retrospective cohort	1999 2008 About 1 year	Not applicable	No	Not Extracted/ 13238 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting, VA Mid-South VISN 9 Data Warehouse, VA Mid-South VISN 9 Data Warehouse, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <18, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, receive regular care in Veterans Health, Administration healthcare system, HIV/AIDS, cancer, end stage respiratory disease, organ transplant during baseline yr, CHF, ESRD, end stage liver disease
Jadzinsky, 2009 [91] Multi-continent Not extracted	RCT	Start year: 2006 End year: 2007 24 wks	Fewer than 10% participants excluded	Yes	2936/1394 Outpatient: primary care, Outpatint: subspecialty care	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), HbA1c < 8% or >12%, BMI >40 kg/m^2, prior treatment, diabetic ketoacidosis or nonketotic hyperosmolar coma, CVD events 6 months prior, LVEF <40%, psychiatric history, alcohol or drug abuse, abnormal metabolic or hematologic test

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Jain, 2006[92] US, Puerto Rico Not extracted	RCT	Neither year reported 56 Wks	Run-in period but number of participants excluded was NR	NR	NR/502 NR	Age <18 or >80 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. failed initial treatment), HbA1c< 7.5% or >11.5%, pregnant, nursing, duration of DM > than 2 years, intolerance to Rosi, Pio or Troglitazone, drug or alcohol abuse, previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin, SU for 3 months or more, use of hydrochlorothiazide, joint injections, niacin greater than 250 mg/day, oral antidiabetic drugs, concurrent participation in another investigational study, serum creatinine level > 1.5mg/dl of men, 1.4 mg/dl for women, 1 + proteinuria , anemia (< 10g/dl women, < 12g/dl men), BMI ≤20kg/m^2 or >45kg/m^2, hypertension, chronic pulmonary disease, history of cancer not in remission for at least 5 years
Johnson, 2005[201] Canada Not extracted	Cohort	Median follow-up periods for each group ranged from 4.6 to 5.6 yeas	Not extracted	No	Not extracted	Age < 30 years, no Type 2 DM, other
Jones, 2003[202] US Not extracted	RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	NR	NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, CHF, history chronic insulin, FPG <140 or >300 mg/dL, prior rosiglitazone study, use on any investigational drug within 30 days

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Kadowaki, 2013[96] Japan NCT00363948	RCT	2006 2008 12	Yes	Yes	Not Extracted/ 149 NR	Age <20 or >=75yr, HbA1c >9.4% for patients receiving an OHA other than met at screening, 10.5% for patients with met only at screening, 10.5% for all patients completing the run-in period, HbA1c <6.4% for patients receiving an OHA other than met at screening, 6.9% for patients with met only at screening, 6.9% for all patients completing the run-in period, Any kidney disease, high serum creatinine levels (male > 100.8umol/l, female>78.7umol/l), FPG>15.0mmol/l at the beginning of the placebo run-in period, not on stable diet and exercise therapy for at least 8 wks, not on met monotherapy for at least 12 wks
Kahler, 2007[203] US Not extracted	Cohort	Start year: 1998 End year: 2001 3 Years	NA	No	> 1500000/39721 VHA Medical facilities	Age <18 years, non-respondents to 1999 LHSVE survey, medical facilities that do not have assays certified by the National Glycohemoglobin Standardization Program, less than 15 month window period after 1 year exposure to drug, alive as of 31 December 2000, fixed one year window of drug exposure
Kahn, 2006[97] Multi-continent Not extracted	RCT	Start year: 2000 End year: 2006 6 Years	No run-in period	Yes	6676/4360 NR	Age <30 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), uncontrolled hypertension, FPG <126 or > 180 mg/dL, history of lactic acidosis
Kaku, 2011[99] Japan NCT00393718	RCT	2006 52	Yes	Yes	Not Extracted/ 411 NR	Age <20 yrs, HbA1c >10.4%, HbA1c <7.4%, not able to self monitor blood glucoses

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Kikuchi, 2012[101] Japan NCT00297063	RCT	2005 2007 28	No	Yes	Not Extracted/ 373 NR	Age <20 - >75, HbA1c <7.4, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Retinopathy, hyperlipidemia w/o statin tx, SBP >=160 or DBP >=100, FPG >=270, BNP >= 60, hemoglobinopathy, edema, unstable or serious angina, MI in past yr, h/o or current heart failure, serious arrhythmia, valvular dis, cardiomyopathy, serious neuropathy requiring tx
Kvapil, 2006[105] Multinational Europe Not extracted	RCT	Neither year reported 16 Wks	No run-in period	NR	NR/341 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, recurrent severe hypoglycemia, anemia, change in dose of meds known to interfere with glucose metabolism, inclusion criteria includes not adequately controlled on metformin
Lavalle-Gonzalez, 2013[106] Multi-continent NCT01106677	RCT	Neither year reported 56	Yes	Yes	Not Extracted/ 1284 NR	Age <18 or >80, HbA1c >10.5, HbA1c <7, Prior or current use of insulin, Any kidney disease, not on MFM (ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose], repeated FPG and/or fasting self-monitored blood glucose (SMBG), ГëÑ15.0 mmol/l during the pretreatment phase, Type 1 diabetes, treatment with a peroxisome proliferator-activated receptor ╬│ agonist, insulin, another SGLT2 inhibitor or any other AHA (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 wks before screening; cardiovascular disease (including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening uncontrolled HTN
Lawrence, 2004[107] UK Not extracted	RCT	12 titration, 12 week maintenance (planned duration)	Not extracted	Yes	Not extracted	Age <45 or >80 years, any liver disease, any kidney disease, history of CVD, HbA1c for diet treated diabetes: <7% or >10% for low-dose ODM: >7.5%, no Type 2 DM, other

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
List, 2009[109] US Canada Mexico, Puerto Rico NCT00263276	RCT	2005 2006 12	Yes	Yes	Not Extracted/ 389 "98 clinical centers"	Age <18, >79, HbA1c >10, HbA1c >7, BMI >40, Prior use of any diabetes treatment, Any kidney disease, C peptide>1.0 ng/ml
Malone, 2003[112] 14 countries not specified Not extracted	randomized, open-label, 2 arm parallel prospective study	Neither year reported 16 Wks	Fewer than 10% of participants were excluded during run-in	Yes	NR/597 subgroup completing test meals	Age <30 or >75 years, HbA1c <125% of upper limit of normal by local lab within 4 wks prior to entry, BMI >40 kg/m^2, not Type 2 DM, not use of single oral agent (metformin or SU) for 3 months prior to study at maximum clinically effective dose for previous 30 days
Malone, 2004[204] US Not extracted	RCT	Neither year reported 32 Wks	Yes	Yes	145/111 NR	Not extracted Age <30 or >80 years, HbA1c <1.3 or >2.0 times normal, BMI >40 kg/m^2, HbA1c value that is less than or greater than 1.3 and 2.0 times the ULN within 30 days before the study, while using 1 or more ODM without insulin for 30 or more days before study start
Malone, 2005 [205] Multinational Europe Not extracted	RCT	Neither year reported 32 wks	Yes	Yes	119/97 NR	Age <30 or >75 years, HbA1c >2.0 times the upper limit of normal, HbA1c <1.3 times the upper limit of normal, used glitazones within 30 days prior to the study, used NPH QD or BID 30-days prior to entry, expected to benefit from prandial control

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Masica, 2013[206] US Not extracted	Retrospective cohort	1998 2009 2.8 - 3.2	Not applicable	No	Not Extracted/ 1921 electronic health record encounters, Baylor Health Care System (BHCS; Dallas, TX) and Christiana Care Health System (CCHS; Newark, DE), Outpatient diagnosis/procedures	Age <21, Prior use of any diabetes treatment, Prior or current use of insulin, ΓÇóPatients with a T2D-related bill with a date of serviceΓëÑ90 days before EHR problem onset date were designated as pre-existing and excluded from the cohort, <90 days of exposure to metformin, sulfonylureas, or thiazolidinediones (or any combination of those three agents) over the study period
Mogensen, 2014[207] Denmark Not extracted	Retrospective cohort	2007 2011 2.1	Not applicable	No	Not Extracted/ 40028 National databases of inpatient, outpatient, medication and mortality information Administrative database, Danish National Patient Registry, Danish Registry of Medicinal Product Statistics, Danish National Population Registry, National Causes of Death Register, Inpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <18, Users of glucose lowering treatment before 1 January 1997 with unknown treatment duration, Prior myocardial infarction (ICD-10: I21-I22, ICD-8: 410), Prior stroke (ICD-10: I61-I64, ICD-8: 431ΓÇô434)

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Nakamura, 2000[115] Japan Not extracted	RCT	3 months (planned duration)	Not extracted	No	Not extracted	Any liver disease, history of CVD, treatment experienced, HbA1c <6.5%, no Type 2 DM, other
Nakamura, 2004[116] Japan Not extracted	RCT	Neither year reported 12 Months	No run-in period	NR	NR/45 Inpatient/hospital	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c > 6.5%, BP <140/90 mm Hg, controlled on diet alone, no history ketoacidosis, c peptide <0.33mmol/L, creatinine <1.5, no BP meds, malignancy, no microalbuminuria, collagen vascular disease, non-diabetic renal disease
Nakamura, 2006[185] Japan Not extracted	RCT	Neither year reported 12 months	No run-in period	NR	NR/68 NR	HbA1c >6.5%, history of ketoacidosis, treatment other than by diet alone, fasting C-peptide level < 0.33 mmol/L, hematuria, non-diabetic renal disease, microalbuminura defined as a median urinary albumin excretion of 20 to 200 ug/min
Nauck, 2007[118] US, Multinational Europe, Multi-continent Not extracted	RCT	Neither year reported 52 Wks	Yes	Yes	2141/1172 NR	Age <18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15 mmol/L, insulin use within 8 wks of screening, history of Type 1 DM, other treatments for hypoglycemia

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Nauck, 2009[119] Multi-continent NCT00286442	RCT	Neither year reported 26	Yes	Yes	Not Extracted/ 527 NR	Age<18 or >80 yr, HbA1c >10.00%, HbA1c <7.00%, BMI <23 or >45 kg/m2, Any kidney disease, used antidiabetic agents other than met within the 3 months prior to screening, or not on ongoing (>=3 months) stable metformin monotherapy regimen (>=1500mg per day for at least 8 wks), C-PEPTIDE CONCENTRATION <0.26 nmol/l, use of steroids or weight loss meds in last 3 months after run-in/stabilisation period FPG>=275mg/dl, during run-in/stabilisation peiod <75% compliance with the single-blind placebo regimen, h/o cardiac surgery or cardiovascular disease in last 6 months, history of cancer (other than squamous cell or basal cell carcinoma of the skin that had not been in full remission for at least 5 years), laser treatment for proliferative diabetic retinopathy within 6 months, history of treated diabetic gastroparesis, New York Heart Association Class 3 or 4 heart failure
Nauck, 2011[120] Multi-continent NCT00660907	RCT	2008 52	Yes	Yes	Not Extracted/ 814 NR	Age < 18 years, HbA1c >10%, HbA1c <6.50%, BMI > 45.0 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, not taking metformin +/- another oral antidiabetes drug, FPG > 15 mmol/L; C-peptide < 0.33 nmol/L, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; polyuria/polydipsia with > 10% weight loss, calculated creatinine clearance < 60 mL/min; urine albumin:creatinine ratio > 203.4 mg/mmol, AST and/or ALT and/or creatine kinase >= 3x ULN; serum total bilirubin > 34 micromol/L, Hb <= 11 g/dL for men and <= 10 g/dL for women; abnormal thyroid stimulating hormone level, SBP >= 180 mmHg and/or DBP >= 110 mmHg, cardiovascular event in last 6 months, CHF, significant respiratory, hematological, oncological, endocrine, immunological, and alcohol and/or substance misuse disorders, use of systemic corticosteroids equivalent to >10 mg of oral prednisolone within 30 days of enrolment, history of bariatric surgery; use of weight loss medication within 30 days or enrolment

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Nauck, 2014[121] NR NCT00734474	RCT	Neither year reported 52	Yes	Yes	Not Extracted/ 1098 NR	Age<18 or >75 years, HbA1c >= 9.5%, HbA1c <8% if on diet and exercise alone or <7% if on OAD monotherapy or combination therapy, BMI <25 or >40 kg/m2, Duration of diabetes <6 months, Prior or current use of insulin, Prior or current use of study drug, unstable weight during the 3-months prior to study entry
Pantalone, 2009 [208] United States Not extracted	Cohort	Start year: 1998 End year: 2006 8 years	NA	Yes	NA/20450 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), on dialysis, on combination ODM, on insulin or other injectible antidiabetics, history of CHF
Pantalone, 2012[209] US Not extracted	Retrospective cohort	1998 2006 2.2	Not applicable	Yes	Not Extracted/ 23915 Inpatient/hospital Outpatient: primary care, Outpatient: subspecialty care setting, Cleveland Clinic EMR including main campus or family health centres, Cleveland Clinic EMR including main campus or family health centres, Inpatient diagnosis/procedure, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <18, Prior or current use of insulin, Prior or current use of study drug, Any kidney disease, does not have at least two encounters for diabetes after visiting the Cleveland Clinic main campus or family health centres, Patients prescribed insulin or other injectable diabetes medications (as monotherapy or in conjunction with oral agents), and those on multiple oral agents at baseline, were excluded.

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Petrica, 2009[126] Romania Not extracted	RCT	Neither year reported 12	No	No	Not Extracted/ 44 Outpatient: subspecialty care setting	HbA1c <7%, < 5 years, no poor glycemic control with previous medication, no stable therapy with metformin for at least 6 months CKD of non-diabetic origin, symptoms or history of, cerebrovascular disease (TIA, stroke), micro/macroalbuminuria, thyroid dysfunction, abnormal albuminuria, microangiogrpahic complications
Pfutzner, 2011[128] Germany (assumed based on author affiliations) NCT00770653	RCT	Neither year reported 24	No	Yes	Not Extracted/ 305 NR	Age <18 - >75, HbA1c <6.5, Any liver disease, Any kidney disease, History of CVD, Pregnant, patients without dyslipidemia, Prior use of any diabetes treatment except for metformin, no current treatment MET, respiratory, neurological or hematlogical disease, not on individually-determined maximal metformin, hypersensitivity to study drugs, history of severe or multiple allergies, h/o significant CVD (greater than NYHA stages II-IV)
Pfutzner, 2011[129] Multi-continent NCT00327015	RCT	Neither year reported 76	Yes	Yes	Not Extracted/ 1306 Community outpatient settings (unspecified)	Age <18 or >77 years, HbA1c >12.00%, HbA1c <8.00%, BMI >40 kg/m2, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, fasting C-peptide < 1.0 ng/ml, symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, CVD event within the prior 6 months or NYHA stage III/IV congestive heart failure and/or LVEF </= 40%, psychiatric disorder, alcohol or drug abuse within previous year, treatment with potential CYP3A4 inhibitors or inducers, immunocompromised individuals, clinically signficant abnormal hepatic, renal, endocrine, metabolic or hematological screening tests
Pratley, 2010 [130] Multi-continent, Europe, USA and Canada Not extracted	RCT	Neither year reported 2 years	No run-in period	Yes	1302/665 “office based”- possibly outpatient	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >7.5% or <10%, BMI >45 kg/m2, no Type 2 DM, cancer, contraindication to trial drugs, recurrent hypoglycemia or hypoglycemia unawareness, not on metformin for at least 3 months, on any non-metformin ODM in past 3 months

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Pratley, 2014[131] Multi-continent NCT01023581	RCT	Neither year reported 26	Yes	Yes	Not Extracted/ 784 NR	Age <18yr or >80 yr, HbA1c >10%, HbA1c <7.50%, BMI <23 or >45 kg/m2, <20 or >35 kg/m2 for Asian participants, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, Not using adequate contraception, class 3 or 4 CHF OR recent CVD event in last 3 months such as MI, stent, bypass, adequate controlled glycemia following treatment with diet and exercise alone for at least 2 months prior to screening, fasting C-peptide concentration < 0.8ng/ml (0.26nmol/l), lack of ability or willingness to monitor blood glucose using a home glucos monitor and keep a glucose diary, at week-1 of the placebo run-in/stabilization period prior to randomization: HbA1c<7.5% or >10%, at week-1 of the placebo run-in/stabilization period prior to randomization: study drug compliance < 75% or >125%, at week-1 of the placebo run-in/stabilization period prior to randomization: use of oral or systemically injected glucocorticoids or weight-loss drugs, low hemoglobin levels (Γëñ 12 and Γëñ 10 g/dL for men and women, respectively), elevated blood pressure (ΓëÑ 150 and ΓëÑ 90 mm Hg for systolic and diastolic, respectively), hemoglobinopathy;
Qiu, 2014[132] Multi-continent NCT01340664	RCT	Neither year reported 22	Yes	Yes	Not Extracted/ 279 NR	Age <18 or >80, HbA1c >10.5 or <7, Any kidney disease, FPG and/or fasting self-monitored blood glucose 15.0 mmol/L during the pretreatment phas, diabetic ketoacidosis, history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident) within 3 months before screening, un- controlled hypertension, not on metformin monotherapy at protocol-specified doses (at least 1500 mg/d (>2000 mg/d preferred), on any other diabetes medication within last 12 wks, not completing the placebo run-in period

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Raz, 2008[188] Multi-continent Not extracted	RCT	Neither year reported 30 Wks	Run-in period but number of participants excluded was NR	Yes	544/190 NR	Age <18 or >78 years, HbA1c <8% after run-in or HbA1c >11% after run-in, BMI <20 kg/m^2 or >43 kg/m^2, pregnant, nursing, insulin within 8 wks prior to screening, PPAR-G or incretin mimetics within 12 wks prior to screening, Type 1 DM, FPG <7.2 mmol/l or >15.6 mmol/L consistently during run-in, no Type 2 DM
Reasner, 2011[135] US NCT00482729	RCT	2007 2009 44	Yes	Yes	Not Extracted/ 1250 NR	Age <18 or >78 years, HbA1c <7.5%, Prior use of any diabetes treatment, Any liver disease, History of CVD, Contraindication or history of intolerance to metformin, No type 2 diabetes, Not on diet/exercise regimen, Finger stick glucose test <7.2 or >17.8 mmol/l, Type 1 diabetes
Ridderstrale, 2014[136] Multi-continent NCT01167881	RCT	2010 2011 104	Yes	Yes	Not Extracted/ 1549 NR	Age <18, HbA1c >10 or <7, BMI>45, Any kidney disease, not on stable dose of MFM IR (>=1500mg/day or max tolerated dose, or max dose according to local label) for at least 12 wks prior to randomization, blood glucose concentration greater than 13 3 mmol/L after an overnight fast during the placebo run-in, confirmed by a second measurement, use of antidiabetes drugs other than metformin immediate release any time during the 12 wks before randomisation

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Rigby, 2010[137] United States, Multi-continent Not extracted	RCT	Start year: 2007 End year: 2008 16 wks	No run-in period	Yes	356/169 NR	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >10% (9.5% if on metformin combination therapy), HbA1c < 7% (6.5% if on metformin combination therapy), BMI > 40 kg/m2, LDL<50mg/dl or TG > = 500 mg/dL, weight loss program with ongoing weight loss or starting an intensive exercise program within 4 wks of screening, need for oral corticosteroids, bile acid sequestrants, or any antidiabetes medications other than metformin, >2 months insulin, not on metformin for >=3 months (1500-2550 mg/day, Type 1 DM and/or ketoacidosis, dysphagia/swallowing disorders, intestinal motility disorders, pancreatitis, HIV/AIDS, drug/alcohol abuse within 2 years, any serious disorder including pulmonary, hepatic, gastrointestinal, uncontrolled endocrine/metabolic, hematologic/oncologic (within 5 years), neurologic, or psychiatric diseases, current treatment with TZD/combo with metformin/colesevelam/fixed-dose combination product including metformin, hospitalization within 14 days of screening
Roden, 2013[139] Multi-continent NCT01177813.	RCT	2010 2012 24	Yes	Yes	Not Extracted/ 899 Inpatient/hospital Outpatient: primary care, Outpatient: subspecialty care setting, academic medical ctrs, hospitals, and private practices	Age <18, <20 in Japan, <18 or >65 in India HbA1c >10 or 9 in Germany or <7, BMI >45, Any kidney disease, diabetes treatment in 12 wks before randomization, uncontrolled hyperglycaemia (glucose concentration >13 3 mmol/L after an overnight fast during the placebo run-in phase and confi rmed by a second measurement),, contraindications to sitagliptin according to the local label,, treatment with antiobesity drugs within 3 months before informed consent, treatment with systemic steroids at time of informed consent, change in dose of thyroid hormones within 6 wks before informed consent, any uncontrolled endocrine disorder apart from type 2 diabetes., did not meet inclusion criteria after placebo run-in

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Rosenstock, 2006[140] Multi-continent Not extracted	RCT	Start year: 2003 to 2004 32 Wks	Yes	Yes	1252/468 multicenter	Age <18 or >70 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or > 11%, FPG >15 mmol/l, hematological disease, uncontrolled hypertension while on antihypertensive treatment, intermittent or chronic use of oral or intravenous corticosteroids, investigators discretion, use of investigational agent within 30 days of the study (or five half live of the investigational drug if longer than 30 days), previous history of severe edema or medically serious fluid related event associated with TZD, acute or chronic metabolic acidosis, history of diabetic ketoacidosis
Rosenstock, 2013[143] Multi-continent NCT00707993	RCT	Neither year reported 52	Yes	Yes	Not Extracted/ 441 NR	Age <65 or >90 yr, HbA1c> 9.0% for patients on diet and exercise therapy alone, 8.0% for patients on oral antidiabetic monotherapy & 9.0% after washout period without medications within 2 wks 6.50%, not able or unwilling to self-monitor blood glucose with a home glucose monitor
Rosenstock, 2013[144] Multi-continent NCT00749190	RCT	Neither year reported 12	Yes	Yes	Not Extracted/ 495 NR	Age <18 or >80, HbA1c >9 if on MFM and one other OAD or >10 if on MFM monotherapy or < 6.5 if on MFM and one other OAD, <7 if on MFM monotherapy, BMI >40, Any liver disease, Any kidney disease, prior treatment that didn't include MFM and one other oral OAD, unchanged antidiabetic therapy for <10 wks prior to screening including stable metformin therapy (ГёÑ1500 mg/day or maximum tolerated dose); diseases of the central nervous system; chronic or clinically relevant acute infections; history of clinically relevant allergy/hypersensitivity; treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months. h/o of MI, CVA, or TIA in past 6 mo HbA1c <7 or >10 at start of placebo run-in history of clinically relevant allergy/hypersensitivity treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Ross, 2012[146] Multi-continent NCT01012037	RCT	2009 2010 12	Yes	Yes	Not Extracted/ 491 NR	Age <18 or > 80yr, HbA1c> 10.0% when taking met alone; 9.5% when taking met and no more than one other oral antidiabetic drug (SU, meglitinide, DPP-4 inhibitor or a-glucosidase inhibitor with unchanged dose for 12 wks prior to informed consent); 10% after the placebo run-in or < 7.00%, BMI > 45kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception total daily dosage of met was not >=1500mg/day or maximum tolerated dose b.i.d., or was on unstable dose (changed within 12 wks prior to randomisation or during the study) treatment within the prevous 3 months with a thiazolidinedione, a GLP-1 receptor agonist, or an antiobesity drug, major cvd event in last 6 months
Roumie, 2012[210] US	Retrospective cohort	2001 2008 0.78 (metformin), 0.61 (sulfonylurea)	Not applicable	No	Not Extracted/ 253690 VA databases linked to Medicare files, VA databases linked to Medicare files, Inpatient diagnosis/ procedures, Outpatient diagnosis/ procedures, Inpatient pharmacy records, Outpatient pharmacy records	Age <18, Prior use of any diabetes treatment, Prior or current use of insulin, Any kidney disease, initiating oral monotherapy before 10/1/2001 or after 9/30/2008, not receiving regular VHA care (a VHA encounter or prescription fill at least once every 180 days) for at least the past 365 days, not a new user (<365 days since filled prescription for oral or injectable diabetic drug), serious mental illness, serious medical conditions identiՈ¼üed at baseline (heart failure, HIV, cancer except for nonmelanoma skin cancer, organ transplantation, end-stage kidney or liver disease, or respiratory failure), baseline serum creatinine level of 133 mol/L (1.5 mg/dL) or greater, cocaine use, combination therapy
Russell-Jones, 2012[147] Multi-continent NCT00676338	RCT	2008 2010 36	No	Yes	Not Extracted/ 820 NR	Adults, HbA1c >11 or <7.1, BMI <23 - >45, Prior use of any diabetes treatment, unstable weight

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Scheller, 2014[211] Denmark	Retrospective cohort	2007 2011 0.9-1.8	Not applicable	No	Not Extracted/ 84756 Administrative database, The Danish National Patient Register - The Danish Register of Medicinal Product Statistics and the National Causes of Death Register, Inpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Age <20, The metformin group was restricted to patients who had not received glucose-lowering drugs prior to the therapy with metformin, DPP-IV inhibitor users were only included if they had not received a glucose-lowering drug, except for metformin, prior to the treatment with sitagliptin, excluded if the duration of treatment with sitagliptin or metformin monotherapy was less than 30 days
Schernthaner, 2015[148] Multi-continent NCT 01215097	RCT	2009 2012 52 wks	Yes	Yes	NR/720 NR	Age <65, HbA1c>9, HbA1c7, any liver disease, any kidney disease, type 1 diabetes, any antihyperglycaemic therapy other than metformin <8 wks before enrollment, glucocorticoids, cytochrome P450 3A4 inducers, history of ketoacidosis or hyperosmolar non-ketonic coma, haemoglobinopathies, cognitive function problems, alcohol or illegal drug abuse
Schernthaner, 2004[149] Europe Not extracted	RCT	12 months (planned duration)	Not extracted	No	Not extracted	Age <35 or >75 years, treatment experienced, HbA1c <7.5% or >11%, no Type 2 DM

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Schramm, 2011[212] Denmark	Retrospective cohort	1997 2006 3.3	Not applicable	No	Not Extracted/ 107806 Administrative database, The National Patient Registry (Denmark) and The Danish Registry of Medicinal Product Statistics Inpatient diagnosis/ Procedures, Outpatient pharmacy records, Death registry	Age >20, initiated single-agent treatment with an IS or metformin
Schumm-Draeger, 2015[151]	RCT	2010 2011 20 wks	Yes	Yes	NR/400 NR	Not on stable dose of MET >=1500mg/day for >= 10 weeks. Weight loss (sx of uncontrolled dm). BP>=160/100. Clinically significant haematological or oncological conditions. Symptoms of poorly-controlled diabetes.
Scott, 2008[153] Multi-continent Not extracted	RCT	Neither year reported 18 Wks	Run-in period but number of participants excluded was NR	Yes	486/273 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c < 7% or >11%, not on 10 wks on stable dose of metformin, insulin use, Type 1 DM, glucose > 270 mg/dL
Seck, 2010[154] NR Not extracted	RCT	Neither year reported 2 years	Run-in period but number of participants excluded NR	Yes	2141/1172 NR	Age <17 or >78 years

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Seino, 2010[155] Japan Not extracted	RCT	Neither year reported 24 wks	Yes	Yes	NR/464 NR	Age <20 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, HbA1c < 7% or >10%, BMI >35 kg/m^2, treated with insulin within 12 wks of the start of the study, receiving or expecting to receive systemic corticosteroids, known hypoglycemia unawareness or recurrent major hypoglycemia unawareness or recurrent major hypoglycemia, no Type 2 DM, treated with diet therapy for less than 8 wks, on more than 1/2 of the recommended maximum dose of an SU (e.g., on more than 2.5 mg of glibenclamide)
Seino, 2012[156] Japan NCT01318109	RCT	2008 2009 12	Yes	Yes	Not Extracted/ 288 outpatient, but not specified	Age <20 or >=65years, HbA1c >=10.4% after 8 wks of observation or <6.9% after 8 wks of observation, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, HbA1c >=10% variation in A1c between week 4 and 8, not receiving metformin at a stable dosage for at least 12 wks plus specific dietary and exercise therapies, administration of any investigational drug, orhter than met, within 12 wks of study initiation, a history/symptoms of lactic acidosis, h/o drug abuse/dependency, severe cardiovascular or pulmonary function impairment or severe pancreatic, cerebrovascular, or hematologic diseases, dehydration, gastrointestinal disorders, malignant tumours, elevated blood pressure (>=180 / 110mmHg
St John Sutton, 2002[159] US Not extracted	RCT	 52 wks (planned duration)	Not extracted	Yes	Not extracted	Age <40 or age >80 years, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Stenlof, 2014[213] NR NCT01081834	RCT	Neither year reported 52	Yes	Yes	Not Extracted/ 587 NR	Age <18 or >80, HbA1c >10 or <7, Prior or current use of study drug, Any kidney disease, if on AHA other than PPAR agonist or combination MFM+SU, FPG >15 mmol/l, h/o type 1 dm, history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident) within 3 months before screening
Stewart, 2006[160] Multinational Europe Not extracted	RCT	Start year: 2003 to 2004 32 Wks	Yes	Yes	1397/526 NR	Age <18 or >70 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or > 9%, drug naive patients with FPG <7 mmol/l or >9 mmol/l, patient on monotherapy with FPG < 6.0 mmol/l or > 8 mmol/l, prior history of exposure to thiazolidinediones within previous 6 months, use of insulin anytime in the past, uncontrolled hypertension
Suzuki, 2014[161] Japan Not extracted	RCT	2009 2012 6 months	No	No	NR/56 Outpatient: subspecialty care setting	Type 1 diabetes. Severe complication of diabetes. Severe renal and liver dysfunction. Pregnant or nursing women and those who might be pregnant. Alcoholism. A history of stroke and cardiovascular events. Any patient whom the investigator judged to be inappropriate for this study.
Umpierrez, 2014[171] Multi-continent NCT01126580	RCT	2010 2012 52	Yes	Yes	NR	Age <18 years, HbA1c >9.50% or <6.50%, <3 months or >5 years, Prior or current use of insulin, Prior or current use of study drug, on more than one oral antihyperglycemic medication(OAM) or on one OAM for <3 months prior to screening., receiving an OAM and taking >50% of the approved maximum daily dose per respective labels in participating countries, have been taking thiazolidinediones or GLP-1 receptor agonists during the 3 months prior to screening, on one oral medication < 3 months

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Weissman, 2005[174] US Not extracted	RCT	Neither year reported 24 wks (planned duration)	Run-in period but number of participants excluded was NR	Yes	1270/766 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% for subjects having received prior combination treatment (metformin + SU), HbA1c >8.5% for subjects having received prior combination treatment (Metformin + SU), BMI <27 kg/m^2, HbA1c < 7% for drug naive or prior monotherapy subjects, HbA1c > 10% for drug naive or prior monotherapy subjects, FPG < 126 mg/dL or >270 mg/dL, anemia, severe edema, prior insulin use within 3 months of study start, non -compliant patient with metformin up-titration
Wheeler, 2013[214] US	Retrospective cohort	2004 2009 1.4-1.7	Not applicable	No	Not Extracted/ 193,172 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting, VA, Inpatient diagnosis/procedures, Outpatient diagnosis/ procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry	Prior use of any diabetes treatment, less than 2 consecutive prescription of SU, MFM or rosi within 200 days between 1/1/2004 and 12/31/2009, veterans who did not have prescriptions for non-diabetes medications during the year before this first prescription for an oral diabetes medication, because for these individuals we could not distinguish whether they were new users of oral diabetes therap, persons without an outpatient visit to a VHA facility in the year before the first prescription for an oral diabetes medication., renal allograft, type 1 diabetes, history of CHF, serum creatinine level ГёÑ132.6 ╬╠ mol/l (or were missing values), initial dm2 prescription not a study drug or started on dual therapy, other medical exclusions including ketoacidosis, diabetic coma, kidney transplant
White, 2014[175] Multi-continent NCT00885378	RCT	2009 2010 12	Yes	Yes	Not Extracted/ 160 outpatient	Age <18 and >78 years, HbA1c >10% or <7%, BMI >45, Pregnant Nursing, not on metformin monotherapy at >=1500 mg for >=8 wks prior to study start, marked polydipsia and polyuria and >10% weight loss<3 months before screening, h/o DKA or HHNC or insulin use in the last year, h/o CVD within 3 months of screening, CHF class 3 or 4 or known EF<=40%, h/o hemoglobinopathies

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Williams-Herman, 2010[177] Multi-continent NCT00103857	RCT	Neither year reported 104	Yes	Yes	Not Extracted/ 1091 NR	Age <18 or >78 years, HbA1c >11% or <7.50%, Any liver disease, Any kidney disease, History of CVD, completed the 54-week base study, >/= 75% compliant in taking study medication, had not developed contraindication to study medication
Xu, 2015[178] China NCT01147627	RCT	2010 2012 48 wks	No	Yes	NR/416 NR	Acute or severe chronic diabetic complications or illnesses (ketoacidosis, hyperosmotic state, lactic acidosis, severe microand macro-vascular complications, and hepatic dysfunction). Presence of glutamic acid decarboxylase antibodies. Use of drugs affecting gastrointestinal motility, weight and glycaemia. History of pancreatitis. Triglyceride (TG) levels ΓëÑ5 mmolL-1. Dody weight not atble over the last 3 months.
Yang, 2011[180] Multinational Asia (China - India – SouthKorea NCT00661362	RCT	Neither year reported 24	Yes	Yes	Not Extracted/ 570 NR	Age <18, HbA1c >10 or <7, Any liver disease, Any kidney disease, Pregnant, Nursing, not on stable dose of metformin; C-peptide <0.33 nmol/l, history of diabetic ketoacidosis or hyperosmolar coma, symptoms of poorly controlled dm, CHF - NYHA III-IV, use of sysetmic steroids or CYP 3A4 inducersHemoglobinopathies, signiifcant cardiovasc illness within 6 mo of enrollment, autoimmune skin d/o, GI surgery that could affect absorpotion, immunocompromised, drug or alcohol abuse in past 12 mo, abnormal lab, exam, ECG that would compromise safe, successful participation - investigator discretion, insulin in past yr, Prior use of any diabetes treatment besides metformin within 8 wks, ever used DPP4 inhib
Yang, 2012[182] China NCT00813995	RCT	2009 2010 24	Yes	Yes	Not Extracted/ 395 NR	Age <18 - >78, HbA1c >11 or <7.5, Any liver disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Diabetes type 1, history of ketoacidosis, CHF, unstable CHD, not Chinese, able to get off other diabetes meds during run-in prior use of TZDs

Author, year Country Registered Protocol	Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Zhang, 2012[187] China Not extracted	RCT	Neither year reported 16	Yes	Yes	Not Extracted/ 42 check up center at hospital	HbA1c >10.00% or <7.00%, Prior or current use of insulin, Any liver disease, History of CVD, did NOT have a 24h urinary albumin level <30 or >300 mg/24h after determination from 2 samples, statins, angiotensin II receptor blocker, angiotensin-converting enzyme inhibitors in the previous 2 wks, had primary nephropathy or secondary kidney disease besides diabetic nephropathy, had rheumatic disease, had acute diabetic complications, patients failed to keep FPG between 4.4-8.0mmol/l and maintain 2h-PG<11.1mmol/l

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table D6. Population characteristics of studies evaluating effects of diabetes medications on long-term outcomes

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Ahren, 2014[2]	Metformin + placebo, 104	56.1	49.5	C: 63.4; AA: 22.8; Asian: 5; H: 31.7	32.8 91.6	8.2	6.7	42
	Metformin + glimepiride + placebo, 317	54.4	51.5	C: 71.7; AA: 12.7; Asian: 5.2; H: 34.9	32.5 91.8	8.1	6	99
	Metformin + sitagliptin + placebo, 313	54.3	46	C: 74.5; AA: 11.6; Asian: 6.6; H: 36.8	32.5 90.3	8.1	5.8	101
	Metformin + abliglutide + placebo, 315	54.3	44.7	C: 70.9; AA: 17.5; Asian: 6; H: 32.8	32.7 89.6	8.1	6	100
Del Prato, 2015[32]	Metformin + glipizide, 401	58.6	54.9	NR	NR 87.6	7.74	6.6	NR
	Metformin + dapagliflozin, 400	58.1	55.3	NR	NR 88.4	7.69	6.1	NR
Suzuki, 2014[161]	Sitagliptin, NR	56.1	56	NR	NR 81.7	9.1	1.9	NR
	Liraglutide, NR	58.6	62	NR	NR 82.3	9.8	2.4	NR
Xu, 2015[178]	Pioglitazone, 136	NR	55.1	NR	NR 70.6	8	NR	18
	Exenatide, 142	NR	67.3	NR	NR 71.7	8	NR	32
Del Prato, 2014[33]	Metformin + glipizide, 874	55.4	50.5	C: 61; AA: 9.3; Asian: 23.2; Other: 6.5	31.1 85.6	7.6	5.53	NR
	Metformin + alogliptin, 880	55.2	47.6	C: 63.3; AA: 8.4; Asian: 21.7; Other: 6.5	31.3 85.3	7.6	5.12	NR
	Metformin + alogliptin, 885	55.5	51.1	C: 62.7; AA: 7.5; Asian: 23.4; Other: 6.4	31.3 86.3	7.6	5.45	NR
Schumm-Draeger, 2015[151]	Metformin + placebo, 101	58.5	46.5	NR	31.74 NR	7.94	5.53	7.9
	Metformin + dapagliflozin, 100	55.3	46.5	NR	33.09 NR	7.78	5.12	6
	Metformin + dapagliflozin, 99	58.5	49.5	NR	32.25 NR	7.71	5.45	9.1
Brownstein,	Pioglitazone, 806	63.7	52	NR	NR NR	8.1	NR	NR

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
2010[191]	Rosiglitazone, 1879	64	51.7	NR	NR NR	8	NR	NR
	Metformin, 12490	61.7	49.9	NR	NR NR	7.8	NR	NR
	Any in the Sulfonylurea class, 11200	65.8	57.5	NR	NR NR	7.7	NR	NR
Seino, 2010[155]	Glibenclamide, 132	58.5	65	Asian: 100	24.4 NR	8.978	8.5	12
	Liraglutide, 268	58.2	68	NR	24.5 NR	8.92	8.1	22
Aschner, 2010[7]	Metformin, 439	55.7	44	NR	30.9 NR	7.2	2.1	75
	Sitagliptin, 455	56.3	48	NR	30.7 NR	7.2	2.6	61
Seck, 2010[154]	Metformin + sitagliptin, 248	57.6	57.3	AA: 3.6, Asian: 9.3, C: 77.4, H: 5.6, O: 4	30.9 88.5 kg	7.3	5.8	231
	Metformin + glipizide, 584	57	62.9	AA: 5.1, Asian: 8.2, C: 78.5, H: 5.1, O: 3.1	31.3 90.3 kg	7.3	5.7	328
Pratley, 2010[130]	Metformin + sitagliptin, 219	55	55	AA: 5, Asian: 1, C: 91, H: 16, O: 4	32.6 93.1 kg	8.5	6.3	25
	Metformin + liraglutide, 221	55.9	52	AA: 10, Asian: 3, C: 82, H: 17, O: 5	32.6 93.7 kg	8.4	6	27
	Metformin + liraglutide, 221	55	52	AA: 7, Asian: 2, C: 87, H: 15, O: 4	33.1 94.6 kg	8.4	6.4	52
Pantalone, 2009[208]	Rosiglitazone, 1079	61.4	45.5	C: 86.8	32.7 NR	7.3	NR	NR
	Any in the Sulfonylurea Class, 7427	66.1	49.5	C: 78	31.1 NR	7.6	NR	NR
	Pioglitazone, 1508	61.6	48.3	C: 83.5	33 NR	7.4	NR	NR
	Metformin, 10436	56.8	41.18	C: 76.9	33.8 NR	7.7	NR	NR
Hsiao, 2009[215]	Metformin, 46444	59	48.22	NR	NR NR	NR	NR	NR

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Rosiglitazone, 2093	61.24	53.46	NR	NR NR	NR	NR	NR
	Pioglitazone, 495	60.75	52.02	NR	NR NR	NR	NR	NR
	Any in the Sulfonylurea class, 97651	60.71	54.1	NR	NR NR	NR	NR	NR
	Metformin + sulfonylurea, 267754	57.17	54.45	NR	NR NR	NR	NR	NR
	Metformin + rosiglitazone, 2408	57.3	49.8	NR	NR NR	NR	NR	NR
Rigby, 2009[137]	Metformin + rosiglitazone, 56	54.7	41.1	AA: 3.6, Asian: 0, C: 28.6, H: 67.9, O: 0	NR 81.1 kg	8.06	7.57	5
	Metformin + sitagliptin, 56	54.8	35.7	AA: 1.8, Asian: 0, C: 23.2, H: 73.2, Unspecified: 1.8	NR 79.6 kg	8.17	8.35	11
Jadzinsky, 2009[91]	Metformin + saxagliptin, 320	52.4	51.6	AA: 2.2, Asian: 15.9, C: 76.9, O: 5	29.9 NR	9.4	2	NR
	Metformin + saxagliptin, 323	52.1	45.2	AA: 2.2, Asian: 16.7, C: 75.2, O: 5.9	30.3 NR	9.5	1.4	NR
	Metformin, 328	51.8	49.7	AA: 1.2, Asian: 15.9, C: 76.5, O: 6.4	30.2 NR	9.4	1.7	NR
	Saxagliptin, 335	52	50.4	AA: 1.8, Asian: 16.7, C: 76.1, O: 5.4	30.2 NR	9.6	1.7	NR
Home, 2009[89]	Rosiglitazone, 2220	58.4	51.4	C: 99.1	31.6 NR	7.9	7	218
	Rosiglitazone + sulfonylurea, 1103	59.8	49	NR	30.3 85.0 kg	8	7.9	NR
	Metformin + sulfonylurea, 1122	59.7	50.6	C: 99.1	NR 84.3 kg	8	7.9	NR
	Metformin + sulfonylurea, 1105	57.2	52.9	C: 98.4	NR 93.3 kg	7.8	6.3	NR
	Metformin + rosiglitazone, 1117	57	53.8	C: 98.9	NR 93.5 kg	7.8	6.1	NR
	Metformin + sulfonylurea, 2227	58.5	51.7	C: 98.7	31.5 NR	7.9	7.1	233
Scott, 2008	Metformin +	54.8	63	Asian: 38, C: 59, Others: 3	30.4	7.7	4.6	2

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
[153]	rosiglitazone, 87				84.9 kg			
	Metformin + sitagliptin, 94	55.2	55	Asian: 38, C: 61, Others: 1	30.3 83.1 kg	7.8	4.9	9
	Metformin, 92	55.3	59	Asian: 39, C: 61	30 84.6 kg	7.7	5.4	9
Raz, 2008[188]	Metformin + sitagliptin, 96	53.6	51	AA: 3, C: 42, H: 32, Multiracial: 22, Not Specified: 1	30.1 81.5 kg	9.3	8.4	18
	Metformin, 94	56.1	41.5	AA: 1, C: 47, H: 25, Multiracial: 25, Not Specified: 2	30.4 81.2 kg	9.1	7.3	16
Hamann, 2008[80]	Metformin + rosiglitazone, 294	58.5	53	C: 94	33 91.4 kg	8	6.3	61
	Metformin + sulfonylurea, 302	59.3	52	C: 95	32.2 88.9 kg	8	6.4	71
Chien, 2007[24]	Metformin + glyburide, 26	60	71	NR	24.2 63.8 kg	8.71	9	5
	Metformin + glyburide, 26	57	62	NR	24.2 61.3 kg	8.85	6.6	5
	Metformin, 25	59	41	NR	25.7 65.6 kg	8.88	6.4	8
Comaschi, 2007[25]	Metformin + pioglitazone, 103	57	45.63	NR	32.2 85.8 kg	8.4	NR	27
	Metformin + sulfonylurea, 80	59.9	55	NR	29.9 81.9 kg	8.6	NR	13
	Pioglitazone + sulfonylurea, 67	62.2	56.72	NR	28.9 78.8 kg	8.7	NR	14
Kahler, 2007[203]	Any in the Sulfonylurea class, 19053	68.2	NR	AA: 12.6, C: 78.6, O: 8.8	29.6 NR	7.2	(<1: 12.8, 1-3: 32.2, 4-10: 33.4, > 11: 20)	NR
	Metformin, 2988	64.9	96.9	AA: 12.7, C: 78.7, O: 8.7	30.4 NR	7	(<1: 20.5, 1-3: 41.5, 4-10: 25.1, >11: 11.6)	NR

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Metformin + sulfonylurea, 13820	65.6	98.1	AA: 13.2, C: 77.5, O: 9.3	30.3 NR	8	(<1: 4.5, 1-3: 21.2, 4-10: 43.3, >11: 29.1)	NR
	TZD, 675	67.1	97.5	AA: 8.7, C: 80.9, O: 10.4	30.7 NR	7.9	(<1: 3.3, 1-3: 18.2, 4-10: 39.9, >11: 37.5)	NR
Nauck, 2007[118]	Metformin + sitagliptin, 588	56.8	57.1	AA: 7, Asian: 8.5, C: 73.5, H: 7.3, O: 3.7	NR NR	7.7	6.5	202
	Metformin + glipizide, 584	56.6	61.3	AA: 6, Asian: 8.4, C: 74.3, H: 7.9, O: 3.4	31.3 89.7 kg	7.6	6.2	172
Hanefeld, 2007[82]	Rosiglitazone, 189	60.6	57.7	AA: 0, C: 97, O: 3	28.8 NR	8.2	6	9
	Glibenclamide, 203	60.1	70.4	AA: 0, C: 99, O: 0.5	28.7 NR	8.2	6.4	13
	Rosiglitazone, 195	60.4	68.2	AA: 0, C: 98.5, O: 1.5	28.7 NR	8.1	5.9	12
	Glibenclamide, 18	53.5	55.6	NR	NR NR	7.8	16.5	NR
Kahn, 2006[97]	Rosiglitazone, 1456	56.3	55.7	AA: 4.2, Asian: 2.7, C: 87.2, H: 5.2, O: 0.7	32.2 91.5 kg	7.36	(<1: 651, 1-2: 758, >2: 47)	539
	Glyburide, 1441	56.4	58	AA: 4.2, Asian: 2.2, C: 89, H: 4.2, O: 0.3	32.2 92 kg	7.35	(<1 year: 637, 1-2: 751, >2: 53)	634
	Metformin, 1454	57.9	59.4	AA: 3.7, Asian: 2.4, C: 89.1, H: 3.8, O: 1	32.1 91.6 kg	7.36	(< 1 year: 673, 1-2: 724, >2: 57)	551
Rosenstock, 2006[140]	Rosiglitazone, 159	50.6	58	AA: 5, Asian: 14, C: 59, H: 19, O: 3	32.8 NR	8.8	2.7	22
	Metformin + rosiglitazone, 155	50.1	57	AA: 6, Asian: 12, C: 54, H: 26	33.2 NR	8.9	2.3	19
	Metformin, 154	51.5	56	AA: 5, Asian: 14, C: 58, H: 21, O: <1	32.5 NR	8.8	2.9	31
Jain, 2006[92]	Pioglitazone, 251	52.1	53	AA: 15.9, Asian: 1.6, C: 61,	32.5	9.2	0.8	117

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
				H: 20.7, O: 0.4, Native American: 0.4	93.9 kg			
	Glyburide, 251	52.1	56.2	AA: 13.5, Asian: 0, C: 65.7, H: 19.9, Native American: 0.4, O: 0.4	32.8 94.3 kg	9.2	0.78	123
Stewart, 2006[160]	Metformin, 272	59	56	AA: <1, Asian: <1, C: 99, H: <1, Native Hawaiian/Other Pacific Islander: <1	30.6 87.2 kg	7.2	3.7	54
	Metformin + rosiglitazone, 254	58.8	55	AA: 0, Asian: 1, C: 98, H: <1, Native Hawaiian/Other Pacific Islander: 0	30.9 88.1 kg	7.2	3.7	50
Bakris, 2006[12]	Metformin + glyburide, 185	58.8	69	C: 76	31.8 90.3 kg	8.3	7.6	5
	Metformin + rosiglitazone, 204	60	63	C: 78	31.6 89.2 kg	8.5	8	10
Kvapil, 2006[105]	Metformin + glibenclamide, 114	58.1	45.6	NR	30.5 84.0 kg	9.4	8.1	5
	Metformin + aspart 70/30, 116	56.4	45.7	NR	30.4 85.1 kg	9.3	6.7	11
Malone, 2005[205]	Metformin + lispro 75/25, 50	59.18	50	NR	29.41 77.82 kg	8.5	13.52	3
	Metformin + glargine, 47	59.63	38	NR	29.64 77.21 kg	8.48	11.9	10
Agarwal, 2005[189]	Pioglitazone, 22	67	100	AA: 14, C: 86	32 97 kg	7.7	16	1
	Glipizide, 22	64	100	AA: 27, C: 73	34 102 kg	7.7	14	3
Malone, 2004[204]	Pooled arms		63	NR	30.9 91.5 kg	8.7	9	NR
	Metformin + lispro 75/25	NR	NR	NR	NR NR	NR	NR	3 during this arm
	Metformin + glargine	NR	NR	NR	NR NR	NR	NR	7
Nakamura,	Pioglitazone, 15	57	60	NR	NR NR	7.9	17.5	NR

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
2004[116]	Glibenclamide, 15	55	53.3	NR	NR NR	7.8	19.2	0
Malone, 2003[112]	Metformin + lispro 75/25, 296	58	57	AA: 0.7, C: 88.9, H: 7.4, O: 3	29.8 83.0 kg	9.17	8.0	25
	Metformin + glibenclamide, 301	59	49	AA: 1, C: 89, H: 6, O: 4	29.6 81.7 kg	9.27	7.4	29
Jones, 2003[202]	Metformin, 82	60	74	NR	28 NR	8.8	6	NR
	Metformin, 22	64	9	NR	23 NR	8.6	6.5	NR
	Metformin + rosiglitazone, 35	62	71	NR	23 NR	9.3	8	NR
	Metformin + rosiglitazone, 141	58	69	NR	28 NR	8.8	6	NR
	Metformin + rosiglitazone, 142	57	57	NR	34 NR	8.8	5	NR
	Metformin, 121	58	70	NR	34 NR	8.7	5	0
Weissman, 2005[174]	Metformin, 384	55.7	NR	NR	33.8 96.7 kg	7.97	NR	95
	Metformin + rosiglitazone, 382	55.5	NR	NR	34.4 98.2 kg	8.05	NR	76
Bailey, 2005[9]	Metformin, 280	57.6	57	AA: <1, Asian: 1, C: 98, O: 1	32.1 89.5 kg	7.5	6.1	44
	Metformin + rosiglitazone, 288	58.1	58	AA: 1, C: 97, Asian: 1, H: 0, O: 1	32.2 90.9 kg	7.4	6	30
Johnson, 2005[201]	Unspecified Sulfonylurea, 2138	67.8	59	NR	NR NR	NR	NR	NR
	Metformin, 923	64.3	52	NR	NR NR	NR	NR	NR
	Metformin + unspecified Sulfonylurea, 1081	62	54	NR	NR NR	NR	NR	NR
Schernthaner, 2004[149]	Placebo + diet + Metformin, 597	56	57.8	NR	31.4 89.7 kg	8.7	3.1	96
	Placebo + diet +	57	52.6	NR	31.2	8.7	3.4	98

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	pioglitazone, 597				88.2 kg			
Hanefeld, 2004[81]	Placebo + unspecified Sulfonylurea + pioglitazone, 319	60	53.6	AA: 0.6, C: 99.4, Asian: 0, H: 0, O: 0	30.2 85.3 kg	8.82	7	259
	Placebo + Metformin + unspecified Sulfonylurea, 320	60	54.7	AA: 0.9, C: 98.4, Asian: 0, H: 0 Other: 0.6	30 84.9 kg	8.8	7.1	279
Lawrence, 2004[107]	Metformin, 20	59.5	60	NR	29.2 NR	NR	NR	NR
	Pioglitazone, 20	60.4	70	NR	30.6 NR	NR	NR	NR
Garber, 2003[64]	Metformin + glyburide, 171	55.6	44	AA: 10.5, C: 77.2, Asian: 0, H: 8.8, O: 3.5	31.4 91.9 kg	8.8	3	NR
	Glyburide, 151	55.3	43.7	AA: 7.3, C: 81.5, Asian: 0, H: 7.9, O: 3.3	31.1 91 kg	8.7	3	NR
	Metformin, 164	54.7	43.3	AA: 6.7, C: 80.5, Asian: 0, H: 9.1, O: 3.7	31.4 92.8 kg	8.5	2.6	NR
Goldstein, 2003[71]	Metformin + glipizide, 87	54.6	58.60	AA: 11.5, C: 72.4, Asian: 0, H: 16.1, O: 0	31.7 94 kg	8.7	5.9	NR
	Glipizide, 84	57.4	64.30	AA: 11.9, C: 71.4, Asian: 2.4, H: 14.3, O: 0	30.6 89.9 kg	8.9	6.5	NR
	Metformin, 76	56.6	61.80	AA: 15.8, C: 65.8, Asian: 1.3, H: 17.1, O: 0	31.6 93.8 kg	8.7	7.3	NR
Bakris, 2003[11]	Rosiglitazone, 104	55.1	72.1	NR	NR NR	9.1	NR	NR
	Glyburide, 99	56.1	71.7	NR	NR NR	9.5	NR	NR
Hallsten, 2002[79]	Diet + rosiglitazone, 14	58.6	71.4	NR	29.3 NR	6.8	NR	NR
	Placebo + diet, 14	57.7	71.4	NR	30.3 NR	6.3	NR	NR
	Diet + Metformin, 13	57.8	61.5	NR	29.9 NR	6.9	NR	NR
St John Sutton,	Rosiglitazone, 104	55.1	75	AA: 5, C: 73, Asian: 0, H: 0, O: 22	67.3% >=27kg/m^2	9.1	5.3	NR

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
2002[159]					86.2 kg			
	Glyburide, 99	56.1	71	AA: 3, C: 76, Asian: 0, H: 0, O: 21	65.7% >=27 kg/m^2 85.1 kg	9.5	6.2	NR
Gomez-Perez, 2002[73]	Placebo + Metformin, 34	53.4	29.4	C: 2.9, H: 76.5, Mestizo: 20.6	28.5 NR	NR	9.1	NR
	Metformin + rosiglitazone, 35	51.7	28.6	C: 0, H: 80, Mestizo: 20	28 NR	NR	11.1	NR
	Metformin + rosiglitazone, 36	54.2	19.4	C: 11.1, H: 72.2, Mestizo: 16.7	27.6 NR	NR	10.7	NR
Amador-Licona, 2000[186]	Glibenclamide, 23	48.2	30.4	NR	30.4 73.2 kg	8.4	4	NR
	Metformin, 28	49.3	39.3	NR	26.8 70.7 kg	8.5	4.5	NR
Fonseca, 2000[55]	Metformin + rosiglitazone, 113	58.3	68.2	AA: 10, C: 77.3, Asian: 0, H: 0, O: 12.7	29.8 NR	8.9	8.3	18
	Placebo + Metformin, 116	58.8	74.3	AA: 3.5, C: 81.4, Asian: 0, H: 0, O: 15	30.3 NR	8.6	7.3	22
	Metformin + rosiglitazone, 119	57.5	62.1	AA: 6.9, C: 80.2, Asian: 0, H: 0, O: 12.9	30.2 NR	8.9	7.5	18
Nakamura, 2000[115]	Pioglitazone, 15	60	46.7	NR	NR NR	7.7	16	NR
	Glibenclamide, 15	61	53.3	NR	NR NR	7.8	14	NR
DeFronzo, 1995[27]	Metformin, 143	53	43.4	NR	29.9 94.4 kg	8.4	6	NR
	Metformin + glyburide, 213	55	46.0	NR	29 92.1 kg	8.8	7.8	NR
	Placebo + glyburide, 209	56	49.3	NR	29.1 92.6 kg	8.5	8.7	NR
	Placebo + Metformin, 210	55	45.7	NR	29.4 92.6 kg	8.9	8.4	NR
Hermann, 1994[86]	Diet + Metformin, 25	60	63	NR	NR 78.6 kg	6.9	4	NR
	Diet + glibenclamide, 21	NR	NR	NR	NR	NR	NR	NR

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
					NR			
	Diet + Metformin + glibenclamide + Other, 54	NR	80.2	NR	NR NR	NR	NR	NR
Alba, 2013[3]	Pioglitazone 54	53.4	42.6	C: 79.6, AA: 16.7, Asian: 1.9, H: 38.9, O: 1.9	NR 86.6kg	7.9	2.4	2
	Sitagliptin 52	54.6	53.8	C: 86.5, AA: 11.5, Asian: 1.9, H: 36.4, O: 0	NR 85.7kg	7.7	2.4	6
Andersson, 2010[190]	Metformin 688	69	62	NR	NR NR	NR	NR	Not applicable
	Sulfonylurea	76	57	NR	NR NR	NR	NR	Not applicable
	Metformin + Sulfonylurea	71	56	NR	NR NR	NR	NR	Not applicable
Arechavaleta, 2011[5]	Metformin + glimepiride + placebo, 519	56.2	53.8	C: 57.4, AA: 1.2, Asian: 21.4, O: 20	NR 82kg	NR	6.7	51
	Metformin + sitagliptin + placebo, 516	56.3	55	C: 57.6, AA: 1.2, Asian: 21.1, O: 20.1	NR 80.6kg	NR	6.8	48
Arjona Ferreira, 2013[6]	Glipizide + placebo 212	64.3	54.9	C: 28.2, AA: 1.4, Asian: 58.5, H: 28.9, O: 12	NR 70.2kg	7.8	10.1	19.8 %
	Sitagliptin + placebo 211	64.8	59.3	C: 29.6, AA: 1.5, Asian: 53.3, H: 33.3, O: 15.5	NR 68.0kg	7.8	10.7	22.3 %
Aschner, 2012[8]	Metformin + sitagliptin 265	53.3	52	NR	NR 84.2kg	8.5	4.8	12
	Metformin + insulin glargine, 250	53.9	50	NR	NR 83.4kg	8.5	3.9	23
Bailey, 2013[10]	Metformin + placebo 137	53.7	55	NR	31.8 NR	8.11	5.8	64
	Metformin + dapagliflozin + placebo, 137	55	51	NR	31.6 NR	7.99	6	55
	Metformin + dapagliflozin, 137	54.3	50	NR	31.4 NR	8.17	6.4	48
	Metformin + dapagliflozin + placebo, 135	52.7	57	NR	31.2 NR	7.92	6.1	40
Barnett, 2012[13]	Glimepiride	56.7	43.4	C: 67.1, Asian: 27.6, O:	NR	8.1	NR	18

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	76			5.3	80.9 kg			
	Linagliptin 151	56.4	36.4	C: 70.2, Asian: 27.8, O: 2	NR 77.0 kg	8.1	NR	32
Bergenstal, 2010[14]	Metformin + pioglitazone + placebo 165	53	48	C: 39, AA: 8, Asian: 24, H: 27, O: 2	NR 88 kg	8.5	6	21 %
	Metformin + sitagliptin + placebo, 166	52	52	C: 30, AA: 12, Asian: 25, H: 30, O: 3	NR 87 kg	8.5	5	13 %
	Metformin + exenatide + placebo, 160	52	56	C: 33, AA: 12, Asian: 23, H: 31, O: 1	32 89 kg	8.6	6	21%
Bolinder, 2012[17]	Metformin + placebo 91	60.8	56	C: 100, AA: 0, A: 0, H: 0, O: 0	31.7 90.9 kg	7.16	5.5	20
	Metformin + dapagliflozin, 91	60.6	55.1	C: 100, AA: 0, A: 0, H: 0, O: 0	32.1 92.1 kg	7.19	6	20
Borges, 2011[18]	Metformin 340	50.7	53	C: 55, AA: 4, Asian: 34, O: 6	NR 90.6 kg	8.6	2.6	154
	Metformin + rosiglitazone, 348	51.5	53	C: 53, AA: 5, Asian: 35, O: 6	NR 87.1 kg	8.6	2.3	131
Cefalu, 2013[20]	Metformin + glimepiride, 484	56.3	55	C: 67, AA: 5, Asian: 19, O: 9	NR 86.5 kg	7.8	6.6	98
	Metformin + canagliflozin, 483	56.4	52	C: 67, AA: 4, Asian: 21, O: 9	NR 86.9 kg	7.8	6.5	88
	Metformin + canagliflozin, 485	55.8	50	C: 69, AA: 4, Asian: 19, O: 9	NR 86.6 kg	7.8	6.7	105
Corrao, 2011[192]	Metformin 21,810	60	53	NR	NR NR	NR	NR	NA
	Sulfonylurea 48,267	64.8	54.4	NR	NR NR	NR	NR	NA
DeFronzo, 2012[31]	Metformin + placebo 129	55.2	47.3	C: 72.1, AA: 6.2, Asian: 3.9, H: 48.8, Other 17.8	30.6 NR	8.5	6	14%
	Metformin + pioglitazone + placebo 130	54.1	46.9	C: 65.4, AA: 6.2, Asian: 8.5, H: 48.5, Other 20	31.3 NR	8.5	5.7	18.5%
	Metformin + pioglitazone + placebo	56.1	48.8	C: 74.4, AA: 4.7, Asian: 7.8, H: 51.9, iOther 13.2	31.4 NR	8.5	7.6	12.4%

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	129							
	Metformin + pioglitazone + placebo 129	54.5	41.1	C: 65.9, AA: 7, Asian: 9.3, H: 47.3, O: 17.8	30.7 NR	8.5	5.7	16.3%
	Metformin + alogliptin + placebo, 128	53.1	52.3	C: 69.5, AA: 4.7, Asian: 10.9, H: 46.9, O: 14.8	31 NR	8.6	6.2	10.2%
	Metformin + alogliptin + placebo, 129	53.7	38.8	C: 62, AA: 3.9, Asian: 11.6, H: 48.8, O: 22.5	31.5 NR	8.6	5.6	9.3%
Diamant, 2010[44]	Metformin + exenatide 164			NR	NR NR	NR	NR	NR
	Metformin + insulin glargine, 157			NR	NR NR	NR	NR	NR
Ekstrom, 2012[193]	Metformin 14697	63.8	55.3	NR	30.7 NR	NR	4.6	NR
	Metformin + basal insulin, 7109	64.6	56.5	NR	31.6 NR	NR	11.6	NR
Erem, 2014[47]	Metformin 20	52.2	30	NR	NR 87.47kg	7.62	NR	1
	Pioglitazone 20	52.5	25	NR	NR 81.93kg	8.03	NR	1
Esposito, 2011[48]	Metformin 55	54.9	50.9	NR	NR 83.5kg	8.1	NR	4
	Pioglitazone 55	54.2	54.5	NR	NR 84.5kg	8	NR	4
Farcasiu, 2011[51]	Metformin + insulin lispro 75/25, 151	58.4	45.7	C: 98.7, AA: 1.3, O: 1.3	NR 85.1kg	8.5	11.5	23
	Metformin + insulin lispro 50/50, 151	57	39.1	C: 99.3, AA: 0.7	32.3 88.6kg	8.6	10.9	23
Ferrannini, 2013[194]	Metformin	58 median	48.8	C: 60, Asian: 35, O: 5	81.1kg median	NR	NR	NR
	Empagliflozin	58 median	49.4	C: 64.2, Asian: 34.6, O: 1.2	76.8kg median	NR	NR	NR
	Empagliflozin	57 median	50	C: 65.9, Asian: 32.9, O: 1.2	81.2kg median	NR	NR	NR

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
Fonseca, 2012[56]	Metformin 144	55.5	51	C: 13, AA: 4, H: 61, O: 23	31 NR	8.4	5.9	25
	Metformin + saxagliptin 138	55.2	41	C: 9, AA: 7, H: 61, O: 23	30.8 NR	8.3	6.5	8
Forst, 2010[57]	Metformin + placebo 71	60.1	62	C: 97, AA: 1, Asian: 1	NR 93.1kg	8.4	6.2	14
	Metformin + glimepiride 65	59.4	63.1	C: 99, AA: 0, Asian: 2	NR 90.5kg	8.2	6.7	4
	Metformin + linagliptin 66	59.6	56.1	C: 100, AA: 0, Asian: 0	NR 90.7kg	8.5	7.3	10
Gallwitz, 2012[61]	Metformin + glimepiride + placebo, 775	59.8	61	C: 85, AA: 2, Asian: 12, O: <1	30.3 86.8 kg	7.7	NR	NR
	Metformin + linagliptin + placebo, 777	59.8	60	C: 85, AA: 3, Asian: 12, O: <1	30.2 86.1 kg	7.7	NR	NR
	Metformin + glimepiride, 514	56	52	C: 91, H: 7, O: 2	32.3 91.1 kg	7.4	5.5	128
	Metformin + exenatide 515	56	56	C: 92, H: 7, O: <1	32.6 92.8 kg	7.5	5.8	174
Garber, 2011[67]	Glimepiride + placebo 248	53.4	54	C: 77, AA: 12, Asian: 4, H: 38, O: 7	NR 93.3 kg	8.2	5.6	151
	Liraglutide + placebo 251	53.7	47	C: 80, AA: 14, Asian: 2, H: 32, O: 5	NR 92.1 kg	8.2	5.2	141
	Liraglutide + placebo 247	52	49	C: 75, AA: 12, Asian: 5, H: 35, O: 8	NR 92.6 kg	8.2	5.3	132
Genovese, 2013[68]	Metformin + placebo 103	57.8	60.2	C: 100	NR 89kg	7.02	5.7	6
	Metformin + pioglitazone, 110	57	59.1	C: 100	NR 88.8kg	6.92	5.8	13
Genovese, 2013[69]	Metformin 29	56.4	65.5	NR	NR 87.8kg	6.8	3.9	3
Genovese, 2013[69]	Pioglitazone + placebo 29	59.1	48.3	NR	NR 84.1kg	6.9	4.4	5
Goke, 2010[70]	Metformin + glipizide 430	57.6	54	C: 84.2, AA: 0, Asian: 15.1, O: 0.7	31.3 88.6 kg	7.7	5.4	283

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Metformin + saxagliptin 428	57.5	49.5	C: 82.2, AA: 0.2, Asian: 17.1, O: 0.5	31.5 88.7 kg	7.7	5.5	263
Haak, 2012[77]	Metformin 144	52.9	56.9	C: 64.6, AA: 0, Asian: 35.4, O: 0	NR 79.9kg	8.7	NR	17
	Metformin 147	55.2	53.1	C: 64.6, AA: 1.4, Asian: 34, O: 0	NR 80kg	8.5	NR	21
	Linagliptin 142	56.2	56.3	C: 68.3, AA: 0, Asian: 31.7, O: 0	NR 79.1kg	8.7	NR	21
	Metformin + linagliptin 143	55.6	51	C: 72, AA: 1.4, Asian: 25.9, O: 0.7	NR 80.8kg	8.7	NR	16
	Metformin + linagliptin 143	56.4	53.8	C: 65.7, AA: 0.7, Asian: 33.6, O: 0	NR 76.7kg	8.7	NR	11
Haak, 2013[78]	Metformin, 170	55.6	54.1	C: 62.4, AA: 0.9, Asian: 36.7	29.2 NR	7.31	NR	NR
	Metformin, 170	55.7	55.7	C: 63.9, AA: 0, Asian: 36.1	29.5 NR	7.76	NR	NR
	Metformin + linagliptin, 225	55.1	55.4	C: 65.2, AA: 0, Asian: 34.8	28.3 NR	7.95	NR	NR
	Metformin + linagliptin, 225	56.8	51.3	C: 71.7, AA: 1.8, Asian: 26.5	29.8 NR	7.34	NR	
	Metformin + linagliptin 171	55.6	54.1	C: 60.4, AA: 0.9, Asian: 38.7	28.5 NR	6.93	NR	NR
	Metformin + linagliptin 171	56.1	61.7	C: 68.3, AA: 0, Asian: 31.7	28.8 NR	8.15	NR	NR
Haring, 2014[83]	Metformin + placebo 207	56	56	C: 55, AA: 1, Asian: 44, O: 0	NR 79.7kg	7.9	NR	21
	Metformin + empagliflozin, 217	55.5	58	C: 52, AA: 2, Asian: 46, O: 1	NR 81.6kg	7.94	NR	8
	Metformin + empagliflozin, 214	55.6	56	C: 53, AA: 0, Asian: 46, O: 1	NR 82.2kg	7.86	NR	18
Henry, 2012[84]	Metformin + placebo, 201	51.8	24	NR	NR 85.6kg	9.2	0.6	30

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Dapagliflozin + placebo, 203	52.3	22	NR	NR 86.2kg	9.1	0.4	33
	Metformin + dapagliflozin, 194	51.7	21	NR	NR 84.1kg	9.2	0.3	17
Henry, 2012[84]	Metformin + placebo, 208	52.7	46.6	NR	NR 87.2kg	9.1	0.5	27
	Dapagliflozin + placebo, 219	51.1	47.9	NR	NR 88.5kg	9.1	0.6	31
	Metformin + dapagliflozin, 211	51	50.2	NR	NR 88.4kg	9.1	0.6	28
Hermans, 2012[87]	Metformin 139	58.6	54.7	C: 97.1, AA: 0.7, Asian: 1.4, O: 0.7	31.2 NR	NR	6.9	32
	Metformin + saxagliptin, 147	58.7	59.9	C: 98.6, AA: 0.7, Asian: 0.7, O: 0	32.1 NR	NR	6	28
Hong, 2013[195]	Metformin + placebo 156	62.8	78.2	NR	NR 69.6kg	7.6	5.6	32
	Glipizide + placebo 148	63.8	77	NR	NR 68.7kg	7.6	5.6	31
Hung, 2012[198]	Metformin 61104	60 median	95	C: 79, AA: 16, H: 4, O: 1	32.3 median	NR	NR	NA
	Sulfonylurea 30550	62 median	97	C: 76, AA: 18, H: 5, O: 1	30.7 median	NR	NR	NA
	Rosiglitazone 1923	64 median	97	C: 72, AA: 16, Asian: 11, O: 1	30.9 median	NR	NR	NA
Hung, 2013[199]	Metformin 595	58.7	46.2	NR	NR NR	NR	NR	NA
	Glyburide 330	60.5	56.4	NR	NR NR	NR	NR	NA
	Glimepiride 234	59.2	55.6	NR	NR NR	NR	NR	NA
Hung, 2013[200]	Metformin 7728	59 median	95	C: 77, AA: 12, O: 11	32 median	NR	NR	NA
	Sulfonylurea 4425	60 median	97	C: 77, AA: 17, O: 8	30 median	NR	NR	NA
	Metformin + Sulfonylurea	58	96	C: 69, AA: 19, O: 13	31 median	NR	NR	NA

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	1000	median						
Kadowaki, 2013[96]	Metformin + placebo 72	57.2	68.1	NR	25 NR	8.4	7.3	 5.6%
	Metformin + sitagliptin 77	59.6	71.4	NR	25.2 NR	8.2	7.7	 1.3%
Kaku, 2011[99]	Glibenclamide	58.5	65.2	Asian: 100	NR 65.4 kg	9.18	8.5	 16.7%
	Liraglutide	58.2	68.3	Asian: 100	NR 66.2 kg	9.32	8.1	 16%
Kikuchi, 2012[101]	Rosiglitazone 160	55	62.9	Asian: 100	24.5 NR	8.9	5	11
	Pioglitazone 159	56	62.3	Asian: 100	24.9 NR	8.8	4.2	22
Lavalle-Gonzalez, 2013[106]	Metformin + placebo 183	55.3	51.4	C: 70.5, AA: 1.6, Asian: 16.4, O: 11.5	NR 86.6kg	8	6.8	28
	Metformin + sitagliptin 366	55.5	47	C: 72.1, AA: 3.6, Asian: 11.2, O: 13.1	NR 87.7kg	7.9	6.8	47
	Metformin + canagliflozin, 368	55.5	47.3	C: 68.5, AA: 4.3, Asian: 13.9, O: 13.3	NR 88.8kg	7.9	6.7	46
	Metformin + canagliflozin, 367	55.3	45	C: 69.8, AA: 3.5, Asian: 16.3, O: 10.4	NR 85.4kg	7.9	7.1	44
List, 2009[109]	Metformin 56	54	48	NR	NR 88 kg	7.6	NR	5
	Dapagliflozin 58	55	48	NR	NR 89 kg	8	NR	3
	Dapagliflozin 47	54	53	NR	NR 86 kg	8	NR	7
Masica, 2013[206]	Metformin 1314	53.9	47.8	C: 60.7, AA: 18.9, H: 6, O: 14.5	35.4 NR	7.97	NR	NA
	Sulfonylurea 209	53.7	50.6	C: 60.6, AA: 19.9, H: 5.3, O: 14.1	36.2 NR	8.06	NR	NA
	TZD 103	53.9	42.8	C: 61.5, AA: 15.1, H: 6.9, O: 16.5	34.7 NR	7.57	NR	NA
Mogensen,	Metformin + Sulfonylurea, 25092	62.3	59.4	NR	NR NR	NR	NR	NA

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
2014[207]	Metformin + dpp-4 inhibitor, 11138	59.7	59.8	NR	NR NR	NR	NR	NA
	Metformin + glp-1 agonist, 4345	54.3	56.1	NR	NR NR	NR	NR	NA
	Metformin + basal insulin, 6858	57.1	60.8	NR	NR NR	NR	NR	NA
Nauck, 2009[119]	Metformin + placebo 104	56	48	C: 76, AA: 7, Asian: 6, H: 24, O: 11	32 NR	8	6	6.7 %
	Metformin + alogliptin 210	54	54.3	C: 76, AA: 6, Asian: 9, H: 32, O: 9	32 NR	7.9	6	13.3 %
	Metformin + alogliptin 213	55	47.4	C: 80, AA: 2, Asian: 8, H: 31, O: 10	32 NR	7.9	6	8 %
Nauck, 2011[120]	Metformin + glipizide 408	59	54.9	C: 80.5, AA: 6, Asian: 8.5, O: 5	31.2 NR	7.7	7	94
	Metformin + dapagliflozin, 406	58	55.3	C: 81.8, AA: 6.5, Asian: 6.8, O: 5	31.7 NR	7.7	6	84
Nauck, 2014[121]	Metformin + placebo 177	55	51	C: 51, AA: 5, Asian: 22, H: 22, O: 0	NR 87 kg	8.1	7	65 %
	Metformin + sitagliptin 315	54	48	C: 50, AA: 2, Asian: 26, H: 21, O: 1	NR 86 kg	8.1	7	77 %
	Metformin + dulaglutide, 302	54	44	C: 54, AA: 4, Asian: 26, H: 17, O: 0	NR 86 kg	8.2	7	59 %
	Metformin + dulaglutide, 304	54	48	C: 52, AA: 5, Asian: 25, H: 18, O: 0	NR 87 kg	8.1	7	66 %
Pantalone, 2012[209]	Metformin 12774	57.7	45.8	C: 74.3	33.6 NR	NR	NR	NA
	Glipizide 4325	66.1	56	C: 74.8	30.8 NR	NR	NR	NA
	Glyburide 4279	67.8	56.3	C: 74.9	30.8 NR	NR	NR	NA
	Glimepiride 2537	65.6	54	C: 80.6	31.1 NR	NR	NR	NA
Petrica, 2009[126]	Metformin + rosiglitazone, 22	63	32	NR	33.55 NR	7.72	10.53	5
	Metformin + glimepiride,	63.2	32	NR	33.58	7.58	10.4	5

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	22				NR			
Pfutzner, 2011[128]	Metformin + pioglitazone	59	66	NR	32.6 NR	NR	6.2	32
	Metformin + glimepiride	59	64	NR	32.5 NR	NR	5.9	29
Pfutzner, 2011[129]	Metformin + placebo, 328	51.8	49.7	C: 76.5, AA: 1.2, Asian: 15.9, O: 6.4	30.2 NR	9.4	1.7	109
	Saxagliptin + placebo, 335	52.1	50.4	C: 76.1, AA: 1.8, Asian: 16.7, O: 5.4	30.2 NR	9.6	1.7	126
	Metformin + saxagliptin, 320	52	51.6	C: 76.9, AA: 2.2, Asian: 15.9, O: 5	29.9 NR	9.4	2	91
	Metformin + saxagliptin, 323	52.1	45.2	C: 75.2, AA: 2.2, Asian: 16.7, O: 5.9	30.4 NR	9.5	1.4	92
Pratley, 2014[131]	Metformin 114	54.6	41.2	C: 74.6, AA: 5.3, Asian: 16.7, O: 3.5	30.2 NR	8.5	3.8	17.5%
	Metformin 111	52.6	45.9	C: 71.2, AA: 5.4, Asian: 18, O: 5.4	30.5 NR	8.39	4.1	14.4%
	Metformin + alogliptin 111	53.7	43.2	C: 68.5, AA: 5.4, Asian: 18, O: 8.1	30.9 NR	8.5	4.1	17.1%
	Metformin + alogliptin 114	54.6	54.4	C: 68.4, AA: 4.4, Asian: 22.8, O: 4.4	31 NR	8.43	4.2	17.5%
	+ alogliptin 112	52.6	42.9	C: 75, AA: 2.7, Asian: 15.2, O: 7.1	30.8 NR	8.3	3.6	20.5%
Qiu, 2014[132]	Metformin + placebo 93	57	49.5	C: 78.5, AA: 4.3, Asian: 9.7, O: 7.5	NR 90.5kg	7.7	7	7
	Metformin + canagliflozin, 93	58.6	43	C: 80.6, AA: 5.4, Asian: 3.2, O: 10.8	NR 91.2kg	7.6	6.7	8
	Metformin + canagliflozin, 93	56.7	47.3	C: 89.2, AA: 1.1, Asian: 6.5, O: 3.2	NR 90.2kg	7.6	7.3	13
Reasner, 2011[135]	Metformin	50	57	C: 79, AA: 14, Asian: 4, H: 30, O: 3	33.7 97.2 kg	9.8	3.2	215
	Metformin + sitagliptin	49.4	56	C: 81, AA: 13, Asian: 3, H: 36, O: 3	32.9 94.7 kg	9.9	3.5	216
Ridderstrale,	Metformin + glimepiride, 780	55.7	54	C: 67, AA: 1, Asian: 32, H: 20, O: 0	NR 83.0kg	7.92	NR	132

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
2014[136]	Metformin + empagliflozin, 769	56.2	56	C: 65, AA: 2, Asian: 33, H: 20, O: <1	NR 82.5kg	7.92	NR	121
Roden, 2013[139]	Sitagliptin, 223	55.1	63	C: 34, AA: 1, Asian: 64, O: O<1	NR 79.3kg	7.85	NR	17
	Empagliflozin, 224	56.2	63	C: 34, AA: 1, Asian: 64, O: 0	NR 78.4kg	7.87	NR	18
	Empagliflozin, 224	53.8	65	C: 33, AA: 3, Asian: 64, O: 0	NR 77.8kg	7.86	NR	20
Rosenstock, 2013[143]	Alogliptin 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02 NR	7.45	5.94	42.9
	Glipizide 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02 NR	7.45	5.94	42.9
Rosenstock, 2013[144]	Metformin + placebo 71	60	47	C: 90, AA: 1, H: 9, O: 0	NR 87.7kg	8	NR	5
	Metformin + sitagliptin 71	58	54	C: 87, AA: 0, A: 0, H: 13, O: 0	NR 88.0kg	8.1	NR	1
	Metformin + empagliflozin, 71	59	47	C: 78, AA: 3, H: 20, O: 0	NR 87.9kg	7.9	NR	5
	Metformin + empagliflozin, 70	59	53	C: 83, AA: 1, H: 16, O: 0	NR 90.5kg	8.1	NR	0
Ross, 2012[146]	Metformin + placebo, 44	59.9	47.7	C: 72.7, Asian: 27.3, O: 0	NR 77.7kg	7.92	NR	1
	Metformin + linagliptin + placebo, 224	58.4	54	C: 62.1, Asian: 36.6, O: 1.3	NR 80.6kg	7.98	NR	10
Roumie, 2012[210]	Metformin 155025	62 median	95	C: 74, AA: 12, H/O: 6	31.9 median NR	NR	NR	NA
	Sulfonylurea 98665	67 median	97	C: 75, AA: 13, H/O: 6	30.2 median NR	NR	NR	NA
Russell-Jones, 2012[147]	Metformin + placebo 246	54	62.6	C: 65, AA: 4.5, Asian: 20.7, H: 8.5, O: 1.2	NR 85.9 kg	8.6	2.6	13.4%
	Pioglitazone + placebo 163	55	59.5	C: 67.5, AA: 2.5, Asian: 20.9, H: 9.2 0	NR 86.1 kg	8.5	2.7	18.4%
	Sitagliptin + placebo 163	52	57.7	C: 69.3, AA: 1.8, Asian: 20.2, H: 8, O: 0.6	NR 88.7 kg	8.5	2.7	14.1%

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Exenatide + placebo 248	54	56	C: 68.1, AA: 2.8, Asian: 22.2, H: 6.5, O: 0.4	NR 87.5 kg	8.5	2.7	15.3 %
Scheller, 2014[211]	Metformin	59	51.6	NR	NR NR	NR	NR	NA
	Sitagliptin	62.5	54.2	NR	NR NR	NR	NR	NA
Schernthaner, 2015[148]	Metformin + glimepiride + placebo, 360	72.7	63.3	C: 98.6, O: 1.4	29.3 NR	7.62	NR	75
	Metformin + saxagliptin + placebo, 360	72.5	60.3	C: 97.8, O: 2.2	29.9 NR	7.58	NR	71
Schramm, 2011[212]	Metformin, 43340	52.5	51	NR	NR NR	NR	NR	NR
	Metformin 2906	65.8	73	NR	NR NR	NR	NR	NR
	Glibenclamide	70.9	70	NR	NR NR	NR	NR	NR
	Glibenclamide 12495	63.2	54	NR	NR NR	NR	NR	NR
	Glipizide	70.5	70	NR	NR NR	NR	NR	NR
	Glipizide 6965	63	54	NR	NR NR	NR	NR	NR
	Glimepiride 36313	60.9	55	NR	NR NR	NR	NR	NR
	Glimepiride	70.9	70	NR	NR NR	NR	NR	NR
Seino, 2012[156]	Metformin + placebo 100	52.1	72	NR	69.89 kg NR	8	6.04	0
	Metformin + alogliptin 92	53.4	65.2	NR	69.47 kg NR	7.89	6.34	1
	Metformin + alogliptin 96	52.3	68.8	NR	69.65 kg NR	8.02	6.62	3
Stenlof, 2014[213]	Sitagliptin 170	55.1	41.5	C: 63.6, AA: 9.2, Asian: 13.8, O: 13.3	NR 85.8kg	8.1	4.5	18
	Canagliflozin	55.3	45.2	C: 69.5, AA: 7.1, Asian:	NR	8	4.3	5

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	170			14.7, O: 8.6	86.9kg			
	Canagliflozin 155	55.7	45.8	C: 69.8, AA: 4.7, Asian: 15.1, O: 10.4	NR 87.6kg	8	4.2	20
Umpierrez, 2014[171]	Metformin + placebo 268	55	45	C: 75, AA: 5, Asian: 8, H: 35, O: 13	33 92 kg	7.6	3	55
	Dulaglutide + placebo 270	56	44	C: 73, AA: 8, Asian: 7, H: 32, O: 11	33 92 kg	7.6	3	52
	Dulaglutide + placebo 269	56	42	C: 75, AA: 6, Asian: 8, H: 33, O: 12	34 93 kg	7.6	3	49
Wang, 2015[173]	Metformin + placebo, 101	56.5	50	Asian: 100	25.8 NR	8	NR	12
	Metformin + linagliptin, 205	55.1	49.8	Asian: 100	25.5 NR	7.99	NR	14
Wheeler, 2013[214]	Metformin 132,306	62.3	95.3	C: 66.6, AA: 10.5, O: 3.1, Missing:19.8	NR NR	7.3 (12.1% missing)	NR	NA
Wheeler, 2013[214]	Glipizide 28,957	66.4	97.4	C: 71.7, AA: 13.1, 15.2 (O: 2.3, Missing: 12.9)	NR NR	7.5 (13.2% missing)	NR	NA
Wheeler, 2013[214]	Glibenclamide 28,156	64.9	97.2	C: 71.3, AA: 11.9, 16.8 (O: 4.2, Missing: 12.6)	NR NR	7.6 (12.9% missing)	NR	NA
Wheeler, 2013[214]	Rosiglitazone 3,753	66.9	97.3	C: 74.6, AA: 9.5, 15.8 (O: 6.0, Missing: 9.8)	NR NR	6.8 (18.0% missing)	NR	NA
White, 2014[175]	Metformin + placebo 86	56.6	52.3	C: 93, AA: 3.5, Asian: 2.3, H: 40.7, O: 1.2	32.5 NR	7.97	6.2	9.3%
	Metformin + saxagliptin 74	53.9	54.1	C: 86.5, AA: 10.8, Asian: 2.7, H: 39.2, O: 0	33.7 NR	7.92	5.8	10.8%
Williams-Herman, 2010[177]	Metformin + placebo	54.1	50	NR	31.9 NR	8.1	4	20
	Metformin + placebo	55.9	46	NR	32.2 NR	8.6	4	27
	Metformin + placebo	54.3	44	NR	31.9 NR	8.5	3.9	26

Author, year	Group, N	Mean age (range), in years	Male, %	Race, n %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c (other measure)	Mean duration of diabetes in years	N of withdrawals
	Sitagliptin + placebo	54.1	58	NR	30.3 NR	8.5	3.7	38
	Metformin + sitagliptin	54.5	50	NR	31.6 NR	8.7	3.7	36
	Metformin + sitagliptin	53.9	37	NR	31.4 NR	8.6	4.4	21
Yang, 2011[180]	Metformin + placebo 287	54.4	48.4	Asian: 100	NR 69.0 kg	7.9	5.1	40
	Metformin + saxagliptin 283	53.8	48.1	Asian: 100	NR 68.9 kg	7.9	5.1	29
Yang, 2012[182]	Metformin + placebo 198	55.1	55	Asian: 100	NR 68.9 kg	NR	7.3	16
	Metformin + sitagliptin 197	54.1	47	Asian: 100	NR 67.9 kg	NR	6.4	23
Zhang, 2012[187]	Metformin + glimepiride 23	52	57	NR	24.8 NR	9	4.1	5
	Metformin + exenatide 19	50.2	53	NR	24.9 NR	8.7	4.2	6

Abbreviations: AA = African American; BHI = biphasic human insulin; BMI = body mass index; C = Caucasian; H = Hispanic; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptidase-1; HbA1c = glycated hemoglobin; kg = kilogram; NA – Not applicaple; NR = Not reported; O = Other; SU = sulfonylurea;

Some data may not have been extracted because the question was not asked.

Table D7. Results of studies evaluating effects of diabetes medications on long-term clinical outcomes

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Ahren, 2014[2]	Grp1: Metformin + placebo Fixed >=1500 mg Grp2: Metformin + glimepiride + placebo Fixed >=1500 mg Titrated 2 mg qdup-titration to 4mg qd	Def: All-cause mortality Incidence Grp1: 1 Incidence Gp2: 3			
Ahren, 2014[2]	Grp1: Metformin + placebo Fixed >=1500 mg Grp2: Metformin + sitagliptin + placebo Fixed >=1500 mg Fixed 100 mg qd	Def: All-cause mortality Incidence Grp1: 1 Incidence Grp2: 1			
Ahren, 2014[2]	Grp1: Metformin + placebo Fixed >=1500 mg Grp2: Metformin + albiglutide + placebo Fixed >=1500 mg Titrated 30 mg qwup-titration to 50 mg qw	Def: All-cause mortality Incidence Grp1: 1 Incidence Grp2: 3			
Alba, 2013[3] RCT	Grp1: Pioglitazone Fixed (30mg) Grp2: Sitagliptin Fixed (100mg) ITT: Yes Followup (wks): 52 NR/unclear	Def:All-cause mortality Incidence Grp1: 0 Persons p NR Incidence Grp2: 0 Persons p NR			
Andersson, 2010[190] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 52 NR/unclear	Def:All-cause mortality Incidence Grp1: 0 Persons p NR Incidence Grp2: 0 Persons p NR			
Andersson, 2010[190] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified	Def:All-cause mortality Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 0 315			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: Yes Followup (wks): 26	Persons p NR			
Andersson, 2010[190] Retrospective cohort	Grp1: Metformin Not specified Grp2: Metformin + su Not specified Not specified ITT: Yes Followup (wks): 52	Def:All-cause mortality Incidence Grp1: Persons p NR Incidence Grp2: 2 315 Persons p NR			
Andersson, 2010[190] Retrospective cohort	Grp1: Metformin Not specified Grp2: Metformin + su Not specified Not specified ITT: Yes Followup (wks): 26	Def:All-cause mortality Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 0 302 Persons p NR			
Andersson, 2010[190] Retrospective cohort	Grp1: SU Not specified Grp2: Metformin + su Not specified Not specified ITT: Yes Followup (wks): 52	Def:All-cause mortality Incidence Grp1: Persons p NR Incidence Grp2: 0 302 Persons p NR			
Andersson, 2010[190] Retrospective cohort	Grp1: SU Not specified Grp2: Metformin + su Not specified Not specified ITT: Yes Followup (wks): 52	Def:All-cause mortality Incidence Grp1: Persons p NR Incidence Grp2: 1 304 Persons p NR			
Arechavaleta, 2011[5] RCT	Grp1: Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2: Metformin + sitagliptin	Def:All-cause mortality Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 1 304 Persons p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	+ placebo Not specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT: Yes Followup (wks): 26				
Arechavaleta, 2011[5] RCT	Grp1: Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2: Metformin + sitagliptin + placebo Not specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT: Yes Followup (wks): 26	Def:All-cause mortality Incidence Grp1: 0 315 Persons p NR Incidence Grp2: 0 302 Persons p NR			
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for	Def:All-cause mortality Incidence Grp1: 2 315 Persons p NR Incidence Grp2: 0 302 Persons p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	patients whose renal status changed from moderate to severe during the study) ITT: Yes Followup (wks): 52				
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: Yes Followup (wks): 52	Def:All-cause mortality Incidence Grp1: 2 315 Persons p NR Incidence Grp2: 1 304 Persons p NR			
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia)	Def:All-cause mortality Incidence Grp1: 0 315 Persons p NR Incidence Grp2: 1 304 Persons p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: Yes Followup (wks): 26				
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: No Followup (wks): 26 Active				
Arjona Ferreira, 2013[6] RCT	Grp1: Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2: Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Aschner, 2010[7]	Grp1: Metformin	Grp1: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Varied, prespecified target dose Start: 500 mg, Max: 2000 mg, Mean: 1903 D: 5 wks Grp2: Sitagliptin Fixed Mean: 100 mg	Grp2: 1 (<1)			
Aschner, 2012[8] RCT	Grp1: Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2: Metformin + insulin glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Aschner, 2012[8] RCT	Grp1: Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2: Metformin + insulin glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Aschner, 2012[8] RCT	Grp1: Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2: Metformin + insulin glargine Not specified (mean baseline	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT: No Followup (wks): 26 Active				
Aschner, 2012[8] RCT	Grp1: Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2: Metformin + insulin glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Bailey, 2005[9] RCT	Grp1: Metformin Varied Start: 2500 mg, Max: 3000 mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 2500mg; Start: 4 mg, Max: 8 mg	Grp1: 0 (0) Grp2: 1 (<1)	Def: CVD mortality/sudden cardiac death Grp1: 0 (0) Grp2: 1 (<1)	Def: CVD morbidity/MI (non-fatal) + pulmonary edema with MI Grp1: 0 (0) Grp2: 1 (<1)	
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mgMedian: 1500 mg) Fixed (2.5 mg) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 NA p Incidence Grp2: 0 NA p			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861	Def:All-cause mortality Incidence Grp1: 1			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin Fixed (Mean: 1854 mgMedian: 2000 mg) Fixed (5.0 mg) ITT: Yes Followup (wks): 52 Passive	Incidence Grp2: 2			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT: Yes Followup (wks): 52 Passive	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2: 1			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mgMedian: 1500 mg) Fixed (2.5 mg) ITT: No Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 1 (0.6) NR p NR Incidence Grp2: 0 (0) NR p NR			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin Fixed (Mean: 1854 mgMedian: 2000 mg) Fixed (5.0 mg)	Def:All-cause mortality Incidence Grp1: 1 (0.6) NR p NR Incidence Grp2: 0 (0) NR p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: No Followup (wks): 26 Active				
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT: Yes Followup (wks): 52 Passive	Def:All-cause mortality Incidence Grp1: Persons p NR Incidence Grp2: 1 (0.3) Persons p NR			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mgMedian: 1500 mg) Fixed (2.5 mg) ITT: Yes Followup (wks): 52 Passive	Def:All-cause mortality Incidence Grp1: Persons p NR Incidence Grp2: 0 (0) Persons p NR			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2: Metformin + dapagliflozin Fixed (Mean: 1854 mgMedian: 2000 mg) Fixed (5.0 mg) ITT: Yes Followup (wks): 52 Passive	Def:All-cause mortality Incidence Grp1: Persons p NR Incidence Grp2: 1 (0.3) Persons p NR			
Bailey, 2013[10] RCT	Grp1: Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg)	Def:All-cause mortality Incidence Grp1: 1 (0.3) Persons p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT: Yes Followup (wks): 52 Passive	Incidence Grp2: 0 (0) Persons p NR			
Bakris, 2006[12] RCT	Grp1: Metformin + rosiglitazone Varied, NS; Varied, glucose: ≤ 6.6 mmol/L Unclear; Start: 4mg D: 3 wks Grp2: Metformin + glyburide Varied, NS; Varied, glucose: ≤ 6.6mmol/L Unclear; Start: 5 mg D: 3 wks	Grp1: 1 (1) Grp2: 0 (0)			
Barnett, 2012[13] RCT	Grp1: Glimepiride Titrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg qd and uptitrated in 1mg increments every 4 wks to 4mg qd max if fassting blood glucose was >110mg/dl (6.1mmol/l)) Grp2: Linagliptin Fixed (5mg qdstarted this at randomization and on for all 52 wks) ITT: Yes Followup (wks): 52 Passive	Def:All-cause mortality Incidence Grp1: 1 (0.3) Persons p NR Incidence Grp2: 1 (0.3) Persons p NR			
Barnett, 2012[13] RCT	Grp1: Glimepiride Titrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg	Def:All-cause mortality Incidence Grp1: 2 Incidence Grp2: 0			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	qd and uptitrated in 1mg increments every 4 wks to 4mg qd max if fassting blood glucose was >110mg/dl (6.1mmol/l)) Grp2: Linagliptin Fixed (5mg qdstarted this at randomization and on for all 52 wks) ITT: No Followup (wks): 52 NR/unclear				
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: No Followup (wks): 52 NR/unclear	Def:All-cause mortality Incidence Grp1: 2 Incidence Grp2: 2			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: Yes Followup (wks): 102 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.7) Incidence Grp2: 2 (1.5)			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin	Def:All-cause mortality Incidence Grp1: 1 (0.7) Incidence Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	+ placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: Yes Followup (wks): 102 NR/unclear				
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: Yes Followup (wks): 102 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.7) Incidence Grp2: 0 (0)			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 4 (1) Incidence Grp2: 4 (1)			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 1 (0.5)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.5) Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2: Metformin + exenatide + placebo	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24				
Bergenstal, 2010[14] RCT	Grp1: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Bergenstal, 2010[14]	Grp1: Metformin + sitagliptin	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	+ placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Incidence Grp1: 1 Incidence Grp2: 0			
Bergenstal, 2010[14] RCT	Grp1: Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2: Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Bolinder, 2012[17] RCT	Grp1: Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment) Grp2: Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Bolinder, 2012[17] RCT	Grp1: Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment) Grp2: Metformin + dapagliflozin	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 1 (1.1)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	(Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT: Yes Followup (wks): 102				
Bolinder, 2012[17] RCT	Grp1: Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment) Grp2: Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT: Yes Followup (wks): 104 Active	Def:All-cause mortality Incidence Grp1: 4 (1) 408 Persons p Incidence Grp2: 0 (0) 406 Persons p			
Borges, 2011[18] RCT	Grp1: Metformin Titrated (Max: 2000 mg/dStart 500mg/d) Grp2: Metformin + rosiglitazone Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT: Yes Followup (wks): 26 Active	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Borges, 2011[18] RCT	Grp1: Metformin Titrated (Max: 2000 mg/dStart 500mg/d) Grp2: Metformin + rosiglitazone	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 1			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT: Yes Followup (wks): 26 Active				
Borges, 2011[18] RCT	Grp1: Metformin Titrated (Max: 2000 mg/dStart 500mg/d) Grp2: Metformin + rosiglitazone Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Borges, 2011[18] RCT	Grp1: Metformin Titrated (Max: 2000 mg/dStart 500mg/d) Grp2: Metformin + rosiglitazone Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Brownstein, 2010[191] Cohort	Grp1: Metformin NS			Def: Hospitalization for acute MI	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Rosiglitazone NS			Grp1: ref Grp2: HR: 3.0 (CI: 2.4-3.7)	
Brownstein, 2010[191] Cohort	Grp1: Rosiglitazone NS Grp2: Sulfonylurea			Def: Hospitalization for acute MI Grp1: HR: 1.3 (CI: 1.0-1.7) Grp2: ref	
Cefalu, 2013[20] RCT	Grp1: Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2: Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (100mg) ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			
Cefalu, 2013[20] RCT	Grp1: Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2: Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (300mg) ITT: Yes Followup (wks): 12				
Chien, 2007[24] RCT	Grp1: Metformin Varied, glucose: 140 mg/dL Start: 1000mg, Mean: 1910 mg, Max: 2000 mg D: 4 wks Grp2: Glyburide Varied, glucose: 140 Start: 10 mg, Mean: 19 mg, Max: 20 mg D: 4 wks	Grp1: 0 (0) Grp2: 0 (0)			
Chien, 2007[24] RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide	Grp1: 0 (0) Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Final mean: 1680 mg; Start: 5 mg, Max: 10 mg, Final mean: 8.4 mg D: 4 wks				
Corrao, 2011[192] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			
Corrao, 2011[192] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			
DeFronzo, 1995[27] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Glyburide Varied Start: 5 mg bid, Max: 10 mg bid	Grp1: 1 (0.5) Grp2: 0 (0)	Def: CVD mortality/Fatal MI Grp1: 1 (0.5) Grp2: 0 (0)		
DeFronzo, 1995[27] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2500 mg; Start: 10 mg, Max: 20 mg	Grp1: 1 (1)) Grp2: 0 (0)			
DeFronzo, 2012[31] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) ITT: No Followup (wks): 24				
DeFronzo, 2012[31] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) ITT: No Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			
DeFronzo, 2012[31] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
DeFronzo, 2012[31] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) ITT: No Followup (wks): 104 NR/unclear	Def:All-cause mortality Incidence Grp1: 5 Persons p NR Incidence Grp2: 5 Persons p NR			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
DeFronzo, 2012[31] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) ITT: Yes Followup (wks): 18	Def:All-cause mortality Incidence Grp1: (0) Incidence Grp2: (0)			
DeFronzo, 2012[31] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) ITT: Yes Followup (wks): 18	Def:All-cause mortality Incidence Grp1: (0) Incidence Grp2: 1 (1.1)			
DeFronzo, 2012[31] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): 24	Def:All-cause mortality Incidence Grp1: (0) Incidence Grp2: (0)			
DeFronzo, 2012[31] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed	Def:All-cause mortality Incidence Grp1: (0) Incidence Grp2: (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	after run in) Fixed (25mg) ITT: No Followup (wks): 24				
DeFronzo, 2012[31] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: No Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 0 p Incidence Grp2: 0 p			
DeFronzo, 2012[31] RCT	Grp1: Metformin + placebo Fixed (Mean: 1937mgwas fixed after stabilization/run-in) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: No Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 0 p Incidence Grp2: 0 p			
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Not applicable (e.g., cohort)	Def:All-cause mortality Incidence Grp1: 23 3246 Person-years p Rate ratio (poisson) 0.77 Incidence Grp2: 304 6916 Person-years p Rate ratio (poisson) 1.95			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks):				
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 644 31497 Person-years p Rate ratio (poisson) 1 (ref) Incidence Grp2: 23 3246 Person-years p Rate ratio (poisson) 0.77			
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 644 31497 Person-years p Rate ratio (poisson) 1 (ref) Incidence Grp2: 118 11619 Person-years p Rate ratio (poisson) 0.65			
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in)	Def:All-cause mortality Incidence Grp1: 644 31497 Person-years p Rate ratio (poisson) 1 (ref) Incidence Grp2: 304 6916 Person-years p Rate ratio (poisson) 1.95			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):				
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 118 11619 Person-years p Rate ratio (poisson) 0.65 Incidence Grp2: 23 3246 Person-years p Rate ratio (poisson) 0.77			
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 118 11619 Person-years p Rate ratio (poisson) 0.65 Incidence Grp2: 304 6916 Person-years p Rate ratio (poisson) 1.95			
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) Grp2: Metformin + alogliptin +	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Yes Followup (wks):				
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 222258 Person-years p NR RH 1 Incidence Grp2: 5263 Person-years p NR RH 1.19 (males); 4.36 (1.34-14.20) females)			
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in) Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1902mgfixed after run in) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 222258 Person-years p NR RH 1 Incidence Grp2: 47604 Person-years p NR RH 1.55			
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1893mgfixed dose after run-in)	Def:All-cause mortality Incidence Grp1: 222258 Person-years p NR RH 1 Incidence Grp2: 48238			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (15mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Person-years p NR RH 1.38			
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1919mgfixed after run in) Fixed (45mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 47604 Person-years p NR RH 1.55 Incidence Grp2: 5263 Person-years p NR RH 1.19 (males); 4.36 (1.34-14.20) females)			
DeFronzo, 2012[31] RCT	Grp1: Metformin + pioglitazone + placebo Fixed (Mean: 1854mgfixed after run-in) Fixed (30mg) Grp2: Metformin + alogliptin + placebo Fixed (Mean: 1851mgfixed after run in) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 48238 Person-years p NR RH 1.38 Incidence Grp2: 5263 Person-years p NR RH 1.19 (males); 4.36 (1.34-14.20) females)			
Del Prato, 2015[32]	Grp1: Metformin + glipizide	Def: All-cause mortality		Def: Unspecified	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Titrated 5,10,20mg Grp2: Metformin + dapagliflozin Titrated 2,5,10mg	Incidence Grp1: 5 (1.2) Incidence Grp2: 2 (0.5)		Incidence Grp1: 0 Incidence Grp2: 0	
Del Prato, 2014[33]	Grp1: Metformin + glipizide Titrated 1823.4 mg Titrated 5 mg Grp2: Metformin + alogliptin Titrated 1825.2 mg Fixed 12.5 mg	Def: All-cause mortality Incidence Grp1: 5(0.6) Incidence Grp2: 3(0.3)	Def: Unspecified Incidence Grp1: NR(0.5) Incidence Grp2: NR(0.2)	Def: Composite outcome Incidence Grp1: NR(1.3) Incidence Grp2: NR(0.7) Def: Nonfatal MI Incidence Grp1: Nr(0.5) Incidence Grp2: NR(0.1) Def: Nonfatal stroke Incidence Grp1: NR(0.3) Incidence Grp2: NR(0.3)	
Del Prato, 2014[33]	Grp1: Metformin + glipizide Titrated 1823.4 mg Titrated 5 mg Grp2: Metformin + alogliptin Titrated 1837.2 mg Fixed 25 mg	Def: All-cause mortality Incidence Grp1: 5(1.2) Incidence Grp2: 2(0.5)	Def: Unspecified Incidence Grp1:NR(0.5) Incidence Grp2: NR(0.2)	Def: Composite outcome Incidence Grp1: NR(1.3) Incidence Grp2: NR(0.9) Def: Nonfatal MI Grp1: NR(0.5) Grp2: NR(0.5) Def: Nonfatal stroke Incidence Grp1: NR(0.3) Incidence Grp2: NR(0.2)	
Diamant, 2010[44] RCT	Grp1: Metformin + exenatide Not specified (continued stable dose) Fixed (2mg weekly) Grp2: Metformin + insulin glargine	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Not specified (continued stable dose) Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT: Yes Followup (wks): 12 Active				
Diamant, 2010[44] RCT	Grp1: Metformin + exenatide Not specified (continued stable dose) Fixed (2mg weekly) Grp2: Metformin + insulin glargine Not specified (continued stable dose) Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT: Yes Followup (wks): 24 Passive	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Ekstrom, 2012[193] Retrospective cohort	Grp1: Metformin Not specified (Median: 1100mg) Grp2: Metformin + basal insulin Not specified (Median: 1700mg) Not specified ITT: Yes Followup (wks): 12	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			
Ekstrom, 2012[193] Retrospective cohort	Grp1: Metformin Not specified (Median: 1100mg) Grp2: Metformin + basal insulin Not specified (Median:	Def:All-cause mortality Incidence Grp1: 7 Incidence Grp2: 3			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	1700mg) Not specified ITT: No Followup (wks): 58				
Ekstrom, 2012[193] Retrospective cohort	Grp1: Metformin Not specified (Median: 1100mg) Grp2: Metformin + basal insulin Not specified (Median: 1700mg) Not specified ITT: Yes Followup (wks): 144	Def:All-cause mortality Incidence Grp1: 7 NA p 0.55 Incidence Grp2: 14 NA p			
Erem, 2014[47] RCT	Grp1: Metformin Titrated (Max: 2000mg4-8 wks of titration then fixed after that - article reported all patients ended up on 2000 mg) Grp2: Pioglitazone Titrated (Max: 45mg according to glycemic controlinitiated at 15mg/day and titrated in first 4-8 wks then fixed after that (ended up 6 pts on 15 mg, 12 pts on 30 mg and 1 pt on 45 mg)) ITT: Yes Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.7) Persons p Incidence Grp2: 1 (0.7) Persons p			
Erem, 2014[47] RCT	Grp1: Metformin Titrated (Max: 2000mg4-8 wks of titration then fixed after that - article reported all patients ended up on 2000 mg)	Def:All-cause mortality Incidence Grp1: 971 NA p NR RH 1.00 REF Incidence Grp2: 818 NA p NR RH 1.25			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Pioglitazone Titrated (Max: 45mg according to glycemic controlinitiated at 15mg/day and titrated in first 4-8 wks then fixed after that (ended up 6 pts on 15 mg, 12 pts on 30 mg and 1 pt on 45 mg)) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear				
Esposito, 2011[48] RCT	Grp1: Metformin Titrated (Max: 1000mg twice dailyend of titration: 36% on 1500 mg/d and 64% on 2000 mg/d) Grp2: Pioglitazone Titrated (Max: 45 mgend of titration period: 27% on 30 mg/d and 72% on 45 mg/d) ITT: No Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 5 Persons p NR Incidence Grp2: 5 Persons p NR			
Ferrannini, 2013[194] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (10mg) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 0 (0) p Incidence Grp2: 0 (0) p			
Ferrannini, 2013[194] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the	Def:All-cause mortality Incidence p RH Incidence p RH 1.64			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks): 114.4				
Ferrannini, 2013[194] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (10mg) ITT: Not applicable (e.g., cohort) Followup (wks): 114.4	Def:All-cause mortality Incidence p RH Incidence p RH 1.59			
Ferrannini, 2013[194] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks): 114.4	Def:All-cause mortality Incidence p RH Incidence p RH 1.68			
Ferrannini, 2013[194] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin	Def:All-cause mortality Incidence Grp1: 1 p Incidence p			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (10mg) ITT: No Followup (wks): 36 NR/unclear				
Ferrannini, 2013[194] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (10mg) ITT: No Followup (wks): 36 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 p Incidence p			
Ferrannini, 2013[194] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (10mg) ITT: No Followup (wks): 36 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 p Incidence p			
Ferrannini, 2013[194] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (25mg) ITT: No Followup (wks): 36 NR/unclear	Def:All-cause mortality Incidence p Incidence p			
Ferrannini, 2013[194] RCT	Grp1: Metformin Titrated (Mean: 1567	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (25mg) ITT: No Followup (wks): 36 NR/unclear	Incidence p Incidence p			
Ferrannini, 2013[194] RCT	Grp1: Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2: Empagliflozin Fixed (25mg) ITT: No Followup (wks): 36 NR/unclear	Def:All-cause mortality Incidence p Incidence p			
Fonseca, 2000[55] RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 8 mg	Grp1: 0 (0) Grp2: 1 (1)	Def: CVD mortality/unclear mortality + Fatal MI Grp1: 0 (0) Grp2: 0 (0)		
Fonseca, 2012[56] RCT	Grp1: Metformin Titrated (Max: 2000 mg/duptitration from 1500 to 2000 mg/d) Grp2: Metformin + saxagliptin Fixed (1500 mg/d) Fixed (5mg/d) ITT: No Followup (wks): 52 NR/unclear	Def:All-cause mortality Incidence p Incidence Grp2: 1 p			
Forst, 2010[57] RCT	Grp1: Metformin + placebo Fixed (17of 70 patients	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2: Metformin + glimepiride Fixed Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) ITT: Yes Followup (wks): 24 NR/unclear	Incidence p Incidence p			
Forst, 2010[57] RCT	Grp1: Metformin + placebo Fixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2: Metformin + linagliptin Fixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT: No Followup (wks): 80	Def:All-cause mortality Incidence Grp1: 1 p Incidence Grp2: 2 p			
Forst, 2010[57] RCT	Grp1: Metformin + glimepiride Fixed Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) Grp2: Metformin + linagliptin Fixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT: Not applicable (e.g., cohort) Followup (wks): 91.52	Def:All-cause mortality Incidence Grp1: 1548 p RH 1 Incidence Grp2: 1546 p RH 1.19			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	NR/unclear				
Gallwitz, 2012[61] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 213 p RH 1 Incidence Grp2: 265 p RH 1.47			
Gallwitz, 2012[61] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Not applicable (e.g., cohort) Followup (wks): 91.52 NR/unclear	Def:All-cause mortality Incidence Grp1: 1548 p RH 1 Incidence Grp2: 947 p RH 1.27			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Gallwitz, 2012[61] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 213 p RH 1 Incidence Grp2: 141 p RH 1.53			
Gallwitz, 2012[61] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 213 p RH 1 Incidence Grp2: 737 p RH 1.3			
Gallwitz, 2012[61]	Grp1: Metformin + glimepiride	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	+ placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Not applicable (e.g., cohort) Followup (wks): 91.52 NR/unclear	Incidence Grp1: 1548 p RH 1 Incidence Grp2: 4081 p RH 1.32			
Gallwitz, 2012[61] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Yes Followup (wks): 44 Active	Def:All-cause mortality Incidence Grp1: 2 (0.3) Incidence Grp2: 1 (0.2)			
Gallwitz, 2012[61] RCT	Grp1: Metformin + glimepiride + placebo Fixed (stable dose of 1500mg	Def:All-cause mortality Incidence Grp1: 5 (1.5)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2: Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT: Yes Followup (wks): 76	Incidence Grp2: 2 (0.6)			
Gallwitz, 2012[62] RCT	Grp1: Metformin + glimepiride Not specified (Mean: 1989 mg) Titrated (Mean: 2.01 mginitial dose 1 mg; could be titrated per attending physician every 4 wks based on maximum tolerated dose and country guidelines) Grp2: Metformin + exenatide Not specified (Mean: 1956 mg) Titrated (Mean: 17.35 micgrogramsMax: 20 microgramsstarted at 5 microgm bid and titrated if possible based on GI sxs) ITT: Yes Followup (wks): 76	Def:All-cause mortality Incidence Grp1: 5 (1.5) Incidence Grp2: 1 (0.3)			
Garber, 2003[64] RCT	Grp1: Metformin Varied Start: 500 mg, max: 2000 mg Grp2: Glyburide	Grp1: 0 (0) Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Varied Start: 2.5 mg, max: 10 mg				
Garber, 2003[64] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 1.25 mg, Max: 20 mg	Grp1: 0 (0) Grp2: 2 (1)			
Garber, 2011[67] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.2 mg) ITT: Yes Followup (wks): 76	Def:All-cause mortality Incidence Grp1: 5 (1.5) Incidence Grp2: 2 (0.6)			
Garber, 2011[67] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.8 mg) ITT: Yes Followup (wks): 76	Def:All-cause mortality Incidence Grp1: 2 (0.6) Incidence Grp2: 1 (0.3)			
Garber, 2011[67] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.2 mg) ITT: Yes Followup (wks): 76	Def:All-cause mortality Incidence Grp1: 2 (0.6) Incidence Grp2: 2 (0.6)			
Garber, 2011[67] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.2 mg) ITT: Yes Followup (wks): 24	Def:All-cause mortality Incidence Grp1: 0 Persons p NR Incidence Grp2: 0 Persons p NR			
Garber, 2011[67] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg)	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Liraglutide + placebo Titrated (Max: 1.8 mg) ITT: Yes Followup (wks): 104 NR/unclear	Incidence Grp1: 1 Incidence Grp2: 0			
Garber, 2011[67] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.8 mg) ITT: Yes Followup (wks): 104 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2: 1			
Garber, 2011[67] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.2 mg) ITT: No Followup (wks): 30	Def:All-cause mortality Incidence Grp1: 1 Persons p NR Incidence Grp2: 0 Persons p NR			
Garber, 2011[67] RCT	Grp1: Glimepiride + placebo Titrated (Max: 8mg) Grp2: Liraglutide + placebo Titrated (Max: 1.8 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence p RH Incidence p RH 1.37			
Genovese, 2013[68] RCT	Grp1: Metformin + placebo Fixed (2550 mg) Grp2: Metformin + pioglitazone Fixed (2550 mg) Fixed (45titrated from 30 mg to 45 mg in first four wks then fixed at 45 for 20 wks) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 2 (0.5) Incidence Grp2: 4 (0.9)			
Genovese, 2013[69]	Grp1: Metformin	Def:All-cause mortality			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Titrated (starting dose of 850mg/day, up-titrated to 1700mg or 2550mg in later visits depending on the glycemic response) Grp2: Pioglitazone + placebo Titrated (Max: 45mgstarting dose of 30mg qd, up-titrated to 45mg qd in later visits in the case of poor response) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear	Incidence Grp1: 239 (35) 1533 Person-years p NR 0.85 Incidence Grp2: 2344 (65) 9570 Person-years p NR 1.00 REF			
Goke, 2010[70] RCT	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Гüä day) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear	Def:All-cause mortality Incidence Grp1: 239 (35) 1533 Person-years p NR 0.85 Incidence Grp2: 759 (49) 4280 Person-years p NR 0.89			
Goke, 2010[70] RCT	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Гüä day) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 2344 (65) 9570 Person-years p NR 1.00 REF Incidence Grp2: 759 (49) 4280 Person-years p NR 0.89			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	NR/unclear				
Goke, 2010[70] RCT	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT: Yes Followup (wks): 26	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			
Goke, 2010[70] RCT	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT: No Followup (wks): 26	Def:All-cause mortality Incidence Grp1: 0 Persons p Incidence Grp2: 0 Persons p			
Goke, 2010[70] RCT	Grp1: Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT: Yes Followup (wks): 26 NR/unclear	Def:All-cause mortality Incidence Grp1: Incidence Grp2: 1			
Goldstein, 2003[71] RCT	Grp1: Metformin Varied	Grp1: 0 (0) Grp2: 0 (0)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Start: 500 mg, Max: 2000 mg Grp2: Glipizide Fixed Start: 15mg bid				
Goldstein, 2003[71] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glipizide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	Grp1: 0 (0) Grp2: 0 (0)			
Gomez-Perez, 2002[73] RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 2 mg bid			Def: CVD morbidity/ischemic heart disease + bundle branch block + tachycardia Grp1: 1 (3) Grp2: 1 (3)	
Gomez-Perez, 2002[73] RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 4 mg bid			Def: CVD morbidity/ischemic heart disease + bundle branch block + tachycardia Grp1: 1 (3) Grp2: 2 (5)	
Haak, 2012[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Linagliptin Fixed (5 mg) ITT: Yes Followup (wks): 26 NR/unclear	Def:All-cause mortality Incidence Grp1: Incidence Grp2:			
Haak, 2012[77] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Linagliptin Fixed (5 mg) ITT: Yes	Def:All-cause mortality Incidence Grp1: 1 Incidence Grp2:			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 26 NR/unclear				
Haak, 2012[77] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Linagliptin Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 0 (0)			
Haak, 2012[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Linagliptin Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 1 (0.5) Incidence Grp2: 0 (0)			
Haak, 2012[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 2 (1.1) Incidence Grp2: 0 (0)			
Haak, 2012[77] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 2 (1.1) Incidence Grp2: 1 (0.6)			
Haak, 2012[77] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Haak, 2012[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 1 (0.5) Incidence Grp2: 1 (0.6)			
Haak, 2012[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 2 (1.1) Incidence Grp2: 1 (0.6)			
Haak, 2012[77] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 1 (0.5) Incidence Grp2: 1 (0.6)			
Haak, 2012[77] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)			
Haak, 2012[77] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 104				
Haak, 2012[77] RCT	Grp1: Linagliptin Fixed (5 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 104	Def:All-cause mortality Incidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)			
Haak, 2012[77] RCT	Grp1: Linagliptin Fixed (5 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:All-cause mortality Incidence Grp1: 3024 (3.6) p NR RR 1.0 REF Incidence Grp2: 49 (4) p NR RR 1.25			
Haak, 2012[77] RCT	Grp1: Linagliptin Fixed (5 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.5) Incidence Grp2: 0			
Haak, 2012[77] RCT	Grp1: Linagliptin Fixed (5 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 24 NR/unclear	Def:All-cause mortality Incidence Grp1: 1 (0.5) Incidence Grp2: 0			
Haak, 2013[78] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg)	Def:All-cause mortality Incidence Grp1: 0 Incidence Grp2: 0			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (5.0 mg) ITT: No Followup (wks): 24 NR/unclear				
Haak, 2013[78] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 26				Def:Cerebrovascular Fatal stroke Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 0 315 Persons p NR
Haak, 2013[78] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: Yes Followup (wks): 26				Def:Cerebrovascular Fatal stroke Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 0 302 Persons p NR
Haak, 2013[78] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 26				Def:Cerebrovascular Fatal stroke Incidence Grp1: 0 177 Persons p NR Incidence Grp2: 1 304 Persons p NR
Haak, 2013[78] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: Yes Followup (wks): 26				Def:Cerebrovascular Fatal stroke Incidence Grp1: 0 315 Persons p NR Incidence Grp2: 0 302 Persons p NR
Haak, 2013[78] RCT	Grp1: Metformin Titrated (Max: 2000 mg)				Def:Cerebrovascular Fatal stroke

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: Yes Followup (wks): 26				Incidence Grp1: 0 315 Persons p NR Incidence Grp2: 1 304 Persons p NR
Haak, 2013[78] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 26 Active				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: 1 315 Incidence Grp2:
Haak, 2013[78] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 26 Active				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: 1 315 Incidence Grp2:
Haak, 2013[78] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT: No Followup (wks): 26 Active				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: 1 315 Incidence Grp2: 1 304
Haak, 2013[78] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 26 Active				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: 1 315 Incidence Grp2:
Hamann, 2008[80]	Grp1: Metformin +	Grp1: 2 (1)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	rosiglitazone Varied, glucose: 6.1 mmol/l Start: 2 g; Start: 4 mg D: 12 wks Grp2: Metformin + sulfonylurea Varied, glucose: 6.1 mmol/l Start: 2 g; Start: 5 mg D: 12 wks	Grp2: 2 (1)			
Hanefeld, 2004[81] RCT	Grp1: Metformin + sulfonylurea Varied; NR Start: 850 mg, Max: 850 mg tid; NR Grp2: Pioglitazone + sulfonylurea Varied; NR Start: 15 mg, Max: 45 mg; NR	Grp1: 2 (1) Grp2: 1 (<1)		Def: Coronary heart diseases/cardiac disorders Grp1: (3.1) Grp2: (4.1)	
Hanefeld, 2007[82] RCT	Grp1: Rosiglitazone Fixed Start: 4 mg D: 12 wks Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1: 0 (0) Grp2: 0 (0)			
Hanefeld, 2007[82] RCT	Grp1: Rosiglitazone Fixed Start: 8 mg D: 12 wks Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Grp1: 0 (0) Grp2: 0 (0)			
Haring, 2014[83] RCT	Grp1: Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label))				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident)

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Fixed (10mg) ITT: No Followup (wks): 26 Active				Incidence Grp1: Incidence Grp2:
Haring, 2014[83] RCT	Grp1: Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Grp2: Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Fixed (25mg) ITT: No Followup (wks): 26 Active				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: Incidence Grp2:
Henry, 2012[84] RCT	Grp1: Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2: Dapagliflozin + placebo Fixed (5mg) ITT: No Followup (wks): 26 Active				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident) Incidence Grp1: Incidence Grp2:
Henry, 2012[84] RCT	Grp1: Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2: Metformin +				Def:Cerebrovascular Not-fatal stroke (ischemic stroke and cerebrovascular accident)

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT: No Followup (wks): 26 Active				Incidence Grp1: Incidence Grp2:
Henry, 2012[84] RCT	Grp1: Dapagliflozin + placebo Fixed (5mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT: Yes Followup (wks): 52 Passive				Def:Cerebrovascular Not-fatal stroke (non-fatal stroke) Incidence Grp1: 1 Incidence Grp2: 1
Henry, 2012[84] RCT	Grp1: Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2: Dapagliflozin + placebo Fixed (10 mg) ITT: Yes Followup (wks): 52 Passive				Def:Cerebrovascular Not-fatal stroke (non-fatal stroke) Incidence Grp1: 1 Incidence Grp2:
Henry, 2012[84] RCT	Grp1: Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT: Yes Followup (wks): 104				Def:Cerebrovascular Other cerebrovascular (cerebral infarction) Incidence Grp1: 4 (0.5) Incidence Grp2: 0 (0)

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Henry, 2012[84] RCT	Grp1: Dapagliflozin + placebo Fixed (10 mg) Grp2: Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT: Yes Followup (wks): 104				Def:Cerebrovascular Not-fatal stroke (not defined) Incidence Grp1: 11 NA p NR RR Incidence Grp2: 3 NA p NR RR 0.27
Hermann, 1994[86] RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glyburide Varied Start: 3.5 mg, Max: 10.5 mg			Def: CVD morbidity/unclear CHD Grp1: 2 (5) Grp2: 3 (9)	
Hermann, 1994[86] RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 1500 mg; Start: 1.75mg, Max: 5.25 mg			Def: CVD morbidity/unclear CHD Grp1: 2(5) Grp2: 10 (14)	
Hermans, 2012[87] RCT	Grp1: Metformin Titrated (1500mgMean: mean additional dose (on top of 1500 mg) was 904 mgadded 500mg qd or bid depending on clinical determination) Grp2: Metformin + saxagliptin Fixed (1500 mg) Fixed (5 mg) ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: 1 Incidence Grp2:
Home, 2009[89]	Grp1: Metformin +	Grp1: 157	Grp1: 71	Def: Fatal and non-fatal	Def: Fatal and non-fatal

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	sulfonylurea Varied, HgbA1c: ≤7.0% Max: 2550 mg; Glibenclamide, Max: 15 mg, Glimepiride, Max: 4 mg D: 8 wks Grp2: Rosiglitazone + metformin or sulfonylurea Varied, HgbA1c: ≤7.0% Start: 4 mg, Max: 8 mg; Metformin, Max: 2550 mg, Glibenclamide, Max: 15 mg, Glimepiride, Max: 4 mg D: 8 wks	Grp2: 136 HR: 0.86 (CI: 0.68 to 1.08), p: 0.19	Grp2: 60 HR: 0.84 (CI: 0.59 to 1·18), p: 0.32	MI Grp1: 56 Grp2: 64 HR: 1.14 (CI: 0.80 to 1·63), p: 0.47	stroke Grp1: 63 Grp2: 46 HR: 0.72 (CI: 0.49 to 1·06), p: 0.10
Hong, 2013[195] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: 1 Incidence Grp2:
Hong, 2013[195] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: 1

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	(HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				Incidence Grp2:
Hong, 2013[195] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: 1 Incidence Grp2:
Hong, 2013[195] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: 1 Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				
Hong, 2013[195] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:
Hong, 2013[195] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l,				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				
Hong, 2013[195] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:
Hong, 2013[195] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				
Hong, 2013[195] RCT	Grp1: Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2: Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:
Horsdal, 2011[196] Case-control	Grp1: Metformin Not specified Grp2: SU Not specified ITT: No Followup (wks): 26 NR/unclear				Def:Cerebrovascular Not-fatal stroke (cerebrovascular accident, not defined) Incidence Grp1: Incidence Grp2:

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Hsiao, 2009[215] Cohort	Grp1: Metformin NS Grp2: Pioglitazone NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 22 (4.51) HR: 1.15 (CI: 0.6 to 2.21) p: 0.6753 Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 44 (8.89) HR: 1.0 (CI: 0.26 to 3.89) p: 0.9954	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 2 (0.41) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 5 (1.03)
Hsiao, 2009[215] Cohort	Grp1: Metformin NS Grp2: Rosiglitazone NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 154 (7.52) HR: 1.79 (CI: 1.39 to 2.3) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 266 (12.71) HR: 2.09 (CI: 1.36 to 3.24) p: 0.0007	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 16 (0.8) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 23 (1.14)
Hsiao, 2009[215] Cohort	Grp1: Metformin NS Grp2: Sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 3721 (3.87) Def: ICD-9-CM	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 318 (0.34) Def: TIA defined by ICD-9-CM diagnostic

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
				diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 1678 (1.76)	codes of hospitalization Grp1: 285 (0.63) Grp2: 940 (0.99)
Hsiao, 2009[215] Cohort	Grp1: Metformin NS Grp2: Metformin + rosiglitazone NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 103 (4.26) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 25 (1.03)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 12 (0.49) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 11 (0.45)
Hsiao, 2009[215] Cohort	Grp1: Metformin NS Grp2: Metformin + sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 1367 (2.97) Grp2: 5910 (2.2) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 484 (1.02) Grp2: 11435 (4.27)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 116 (0.25) Grp2: 588 (0.22) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 285 (0.63) Grp2: 1637 (0.61)
Hsiao, 2009[215] Cohort	Grp1: Rosiglitazone NS Grp2: Pioglitazone NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 154 (7.52) Grp2: 22 (4.51) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 266 (12.71)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 16 (0.8) Grp2: 2 (0.41) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 23 (1.14) Grp2: 5 (1.03)

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
				Grp2: 44 (8.89)	
Hsiao, 2009[215] Cohort	Grp1: Pioglitazone NS Grp2: Sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 22 (4.51) Grp2: 3721 (3.87) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 44 (8.89) Grp2: 1678 (1.76)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 2 (0.41) Grp2: 318 (0.34) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 5 (1.03) Grp2: 940 (0.99)
Hsiao, 2009[215] Cohort	Grp1: Rosiglitazone NS Grp2: Sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 154 (7.52) Grp2: 3721 (3.87) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 266 (12.71) Grp2: 1678 (1.76)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 16 (0.8) Grp2: 318 (0.34) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 23 (1.14) Grp2: 940 (0.99)
Hsiao, 2009[215] Cohort	Grp1: Metformin + rosiglitazone NS Grp2: Metformin + sulfonylurea NS			Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalization Grp1: 103 (4.26) Grp2: 5910 (2.2) Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 25 (1.03) Grp2: 11435 (4.27)	Def: ICD-9-CM diagnostic codes of hospitalization Grp1: 12 (0.49) Grp2: 588 (0.22) Def: TIA defined by ICD-9-CM diagnostic codes of hospitalization Grp1: 11 (0.45) Grp2: 1637 (0.61)
Hung, 2012[198] Retrospective	Grp1: Metformin Not specified				Def:Cerebrovascular Other cerebrovascular

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
cohort	Grp2: Rosiglitazone Not specified ITT: Yes Followup (wks): 24				(transient ischemic attack NOS) Incidence Grp1: Incidence Grp2: 1 NA p NR
Hung, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: Rosiglitazone Not specified ITT: NR Followup (wks): 24 NR/unclear				Def:Cerebrovascular Other cerebrovascular (CVA) Incidence Grp1: Incidence Grp2: 1
Hung, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: Rosiglitazone Not specified ITT: NR Followup (wks): 24 NR/unclear				Def:Cerebrovascular Other cerebrovascular (CVA) Incidence Grp1: Incidence Grp2:
Hung, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: Rosiglitazone Not specified ITT: Yes Followup (wks): 144				Def:Cerebrovascular Not-fatal stroke (no specific definition but confirmed by medical record) Incidence Grp1: 10 Incidence Grp2: 15
Hung, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: Rosiglitazone Not specified ITT: Yes Followup (wks): 168				Def:Cerebrovascular Other cerebrovascular (cerebrovascular incident) Incidence Grp1: Incidence Grp2: 1 (4)
Hung, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: No				Def:Cerebrovascular Other cerebrovascular (not clearly predefined (just said 'cerebrovascular

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 80				events'stem infarction) Incidence Grp1: 3 Persons p Incidence Grp2: 5 (1) Persons p
Hung, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 76				Def:Cerebrovascular Other cerebrovascular (death due to ischemic stroke or cerebrovascular accident) Incidence Grp1: 1 p Incidence Grp2: 1 p
Hung, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 76				Def:Cerebrovascular Other cerebrovascular (death due to ischemic stroke or cerebrovascular accident) Incidence Grp1: 1 p Incidence p
Hung, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 76				Def:Cerebrovascular Other cerebrovascular (death due to ischemic stroke or cerebrovascular accident) Incidence Grp1: 1 p Incidence p
Hung, 2012[198] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 76				Def:Cerebrovascular Other cerebrovascular (death due to ischemic stroke or cerebrovascular accident) Incidence Grp1: 1 p Incidence p
Hung, 2012[198] Retrospective	Grp1: SU Not specified				Def:Cerebrovascular Other cerebrovascular

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
cohort	Grp2: Rosiglitazone Not specified ITT: Yes Followup (wks): 76				(death due to ischemic stroke or cerebrovascular accident) Incidence Grp1: 1 p Incidence p
Hung, 2012[198] Retrospective cohort	Grp1: SU Not specified Grp2: Rosiglitazone Not specified ITT: No Followup (wks): 30				Def:Cerebrovascular Fatal stroke Incidence Grp1: 1 p Incidence p
Hung, 2012[198] Retrospective cohort	Grp1: SU Not specified Grp2: Rosiglitazone Not specified ITT: Yes Followup (wks): 104				Def:Cerebrovascular Other cerebrovascular (transient ischemic attack) Incidence Grp1: 1 Incidence Grp2:
Hung, 2012[198] Retrospective cohort	Grp1: SU Not specified Grp2: Rosiglitazone Not specified ITT: Yes Followup (wks): 104				Def:Cerebrovascular Fatal stroke Incidence Grp1: 1 Incidence Grp2:
Hung, 2012[198] Retrospective cohort	Grp1: SU Not specified Grp2: Rosiglitazone Not specified ITT: No Followup (wks): 26				Def:Cerebrovascular Other cerebrovascular (Cerebrovascular accident) Incidence Grp1: 1 (1) Persons p Incidence Grp2: 1 (1) Persons p
Hung, 2013[199] Retrospective cohort	Grp1: Metformin Not specified Grp2: Glyburide Not specified				Def:Cerebrovascular Other cerebrovascular (Cerebrovascular accident)

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: No Followup (wks): 26				Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p
Hung, 2013[199] Retrospective cohort	Grp1: Metformin Not specified Grp2: Glimepiride Not specified ITT: No Followup (wks): 26				Def:Cerebrovascular Other cerebrovascular (Cerebrovascular accident) Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p
Hung, 2013[200] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2: 1	
Hung, 2013[200] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2: 1	
Hung, 2013[200] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2:	
Hung, 2013[200] Retrospective cohort	Grp1: Metformin Not specified Grp2: Metformin + su Not specified Not specified ITT: No			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2:	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 26 Active				
Hung, 2013[200] Retrospective cohort	Grp1: Metformin Not specified Grp2: Metformin + su Not specified Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2:	
Hung, 2013[200] Retrospective cohort	Grp1: Metformin Not specified Grp2: Metformin + su Not specified Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2:	
Hung, 2013[200] Retrospective cohort	Grp1: SU Not specified Grp2: Metformin + su Not specified Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2: 1	
Hung, 2013[200] Retrospective cohort	Grp1: SU Not specified Grp2: Metformin + su Not specified Not specified ITT: No Followup (wks): 26 Active			Def:CVD morbidity Nonfatal MI (unspecified) Incidence Grp1: Incidence Grp2: 1	
Hung, 2013[200] Retrospective cohort	Grp1: SU Not specified Grp2: Metformin + su Not specified Not specified			Def:CVD morbidity Nonfatal MI (non-fatal MI) Incidence Grp1: 1 Incidence Grp2: 3	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: Yes Followup (wks): 52 Active				
Jadzinsky, 2009[91] RCT	Grp1: Metformin Varied, NS Start: 500 mg, Max: 1000 mg D: 1 week Gpr2: Saxagliptin Fixed	Grp1: 3 (1) Grp2: 0 (0)			
Jadzinsky, 2009[91] RCT	Grp1: Metformin + saxagliptin Varied, prespecified target dose; Fixed Start: 500 mg, Max: 1000 mg; Mean: 10 mg D: 1 week Grp2: Metformin Varied, NS Start: 500 mg, Max: 1000 mg D: 1 week	Grp1: 0 (0) Grp2: 3 (1)			
Jadzinsky, 2009[91] RCT	Grp1: Metformin + saxagliptin Varied, prespecified target dose; Fixed Start: 500 mg, Max: 1000 mg; Mean: 5 mg Grp2: Metformin Varied, NS Start: 500 mg, Max: 1000 mg D: 1 week	Grp1: 0 (0) Grp2: 3 (1)			
Jain, 2006[92] RCT	Grp1: Pioglitazone Varied, glucose: 69-141 mg/dL Start: 15 mg, Median: 45 mg, Max: 45 mg D: 12 wks Grp2: Glyburide Varied, glucose: 69-141 mg/dL Start: 5 mg, Median: 10 mg, Max: 15 mg	Grp1: 0 (0) Grp2: 2 (0.8)		Def: Non-fatal MI Grp1: 2 (0.8) Grp2: 2 (0.8)	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	D: 12 wks				
Johnson, 2005[201] Cohort	Grp1: Metformin Varied Min: 250 mg Grp2: Sulfonylurea Varied		Def: CVD mortality/CVD mortality registry + CVD mortality + ICD-9 codes 410, 411-414, 420-427, 429, 428, 430-432, 433-434, 436-438, 440 Grp1: 14.4/1000 patient-years Grp2: 25.5/1000 patient-years	Def: Non-fatal cardiovascular hospitalization/used ICD-9 codes 410-414, 420-427, 429, 428, 440, 430-432, 433-434, 436-438 Grp1: 53.7/1000 patient-years Grp2: 75.3/1000 patient-years	
Jones, 2003[202] RCT	Grp1: Metformin Fixed Start: 2.5 g Grp2: Metformin + rosiglitazone Fixed; Varied, NS Start: 2.5 g; Max: 8 mg	Grp1: 0 (0) Grp2: 1 (1)			
Kadowaki, 2013[96] RCT	Grp1: Metformin + placebo Fixed (maintained previous dosage40% on 500 mg/day; 56% on 750 mg/day; 3% on 1000 mg/day; 1.4% on 1500 mg/day) Grp2: Metformin + sitagliptin Fixed (maintained previous dosage43% on 500 mg/day; 51% on 750 mg/day; 3% on 1000mg/day; 4% on 1500 mg/day) Fixed (50mg qd) ITT: Yes Followup (wks): 52 Active			Def:CVD morbidity Other CVD morbidity (unstable angina) Incidence Grp1: Incidence Grp2: 2	
Kadowaki, 2013[96] RCT	Grp1: Metformin + placebo Fixed (maintained previous dosage40% on 500 mg/day;			Def:CVD morbidity Nonfatal MI (non-fatal MI)	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	56% on 750 mg/day; 3% on 1000 mg/day; 1.4% on 1500 mg/day) Grp2: Metformin + sitagliptin Fixed (maintained previous dosage43% on 500 mg/day; 51% on 750 mg/day; 3% on 1000mg/day; 4% on 1500 mg/day) Fixed (50mg qd) ITT: Yes Followup (wks): 52 Active			Incidence Grp1: 1 Incidence Grp2:	
Kahler, 2007[203] Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR	Grp1: 82 (2.7) Grp2: 1005 (5.3)			
Kahler, 2007[203] Cohort	Grp1: Metformin NR Grp2: Metformin + sulfonylurea NR	Grp1: 82 (2.7) Grp2: 468 (3.4)			
Kahn, 2006[97] RCT	Grp1: Metformin Varied, glucose: 140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Rosiglitazone Varied, glucose: 140 mg/dL Start: 4 mg, Max: 8 mg	Grp1: 31 (2) Grp2: 34 (2)	Def: Fatal MI Grp1: 2 (0.1) Grp2: 2 (0.1)	Grp1: 21 (1.4) Grp2: 25 (1.7)	Def: Stroke not defined Grp1: 19 (1.3) Grp2: 16 (1.1)
Kahn, 2006[97] RCT	Grp1: Metformin Varied, glucose: 140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied, glucose: 140 mg/dL Start: 2.5 mg, Max: 15 mg	Grp1: 31 (2) Grp2: 31 (2)	Def: Fatal MI Grp1: 2 (0.1) Grp2: 3 (0.2)	Def: Not defined Grp1: 21 (1.4) Grp2: 15 (1)	Def: Stroke not defined Grp1: 19 (1.3) Grp2: 17 (1.2)
Kahn, 2006[97] RCT	Grp1: Rosiglitazone Varied, glucose: 140 mg/dL Start: 4 mg, Max: 8 mg Grp2: Glyburide Varied, glucose: 140 mg/dL	Grp1: 34 (2) Grp2: 31 (2)	Def: Fatal MI Grp1: 2 (0.1) Grp2: 3 (0.2)	Def: Non-fatal MI Grp1: 25 (1.7) Grp2: 15 (1)	Def: Stroke not defined Grp1: 16 (1.1) Grp2: 17 (1.2)

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Start: 2.5 mg, Max: 15 mg				
Kaku, 2011[99] RCT	Grp1: Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide Titrated (Max: 0.9 mg/d) ITT: Yes Followup (wks): 52 Active			Def:CVD morbidity Other CVD morbidity (unstable angina) Incidence Grp1: Incidence Grp2: 2	
Kaku, 2011[99] RCT	Grp1: Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide Titrated (Max: 0.9 mg/d) ITT: No Followup (wks): 26			Def:CVD morbidity CVD morbidity composite outcome (see comments) Incidence p Incidence p	
Kaku, 2011[99] RCT	Grp1: Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide Titrated (Max: 0.9 mg/d) ITT: No Followup (wks): 26			Def:CVD morbidity CVD morbidity composite outcome (see comments) Incidence p Incidence p	
Kaku, 2011[99] RCT	Grp1: Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2: Liraglutide Titrated (Max: 0.9 mg/d) ITT: No Followup (wks): 26			Def:CVD morbidity CVD morbidity composite outcome (see comments) Incidence p Incidence p	
Kvapil, 2006[105] RCT	Grp1: Metformin + sulfonylurea Fixed; Varied Start: 1660 mg; Start: 1.75 mg, Max: 10.5, Mean: 6.58 Grp2: Metformin + aspart 70/30 Fixed; Varied Start: 1660 mg; Start: 0.2 U/kg BID, Mean: 0.3 BID	Grp1: 0 (0) Grp2: 1	Def: Fatal MI Grp1: 0 (0) Grp2: 1		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Lavalle-Gonzalez, 2013[106] RCT	Grp1: Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: Yes Followup (wks): 52 Active			Def:CVD morbidity Nonfatal MI (not specified) Incidence Grp1: 1 Incidence Grp2: 0	
Lavalle-Gonzalez, 2013[106] RCT	Grp1: Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: Yes Followup (wks): 104			Def:CVD morbidity Nonfatal MI (not defined) Incidence Grp1: 10 NA p NR RR Incidence Grp2: 6 NA p NR RR 0.6	
Lavalle-Gonzalez, 2013[106] RCT	Grp1: Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2: Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: Yes Followup (wks): 104			Def:CVD morbidity CVD morbidity composite outcome (Must have one of following: cardiovascular death, myocardial infarction, stroke, admission to hospital due to unstable angina) Incidence Grp1: 26 NA p NR RR Incidence Grp2: 12 NA p NR RR 0.46	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Lavalle-Gonzalez, 2013[106] RCT	Grp1: Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: Yes Followup (wks): 104			Def:CVD morbidity Other CVD morbidity (Admission to hospital due to unstable angina) Incidence Grp1: 3 NA p NR RR Incidence Grp2: 3 NA p NR RR 1	
Lavalle-Gonzalez, 2013[106] RCT	Grp1: Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2: Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: No Followup (wks): 50			Def:CVD morbidity Other CVD morbidity (acute MI) Incidence Grp1: Incidence Grp2:	
Lawrence, 2004[107] RCT	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg tid Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp1: 1 (5) Grp2: 0 (0)	Def: CVD mortality/Fatal MI Grp1: 1 (5) Grp2: 0 (0)	Def: CVD morbidity/MI (non-fatal) Grp1: 0 (0) Grp2: 0 (0)	
List, 2009[109] RCT	Grp1: Metformin Titrated (Max: 1500 mg/d) Grp2: Dapagliflozin Fixed (5mg)			Def:CVD morbidity Unspecified CVD morbidity outcomeincreased	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: Yes Followup (wks): 12 Active			blood glucose Incidence Grp1: 0 Incidence Grp2: 0	
List, 2009[109] RCT	Grp1: Metformin Titrated (Max: 1500 mg/d) Grp2: Dapagliflozin Fixed (10 mg) ITT: Yes Followup (wks): 12 Active			Def:CVD morbidity Unspecified CVD morbidity outcomeincreased blood glucose Incidence Grp1: 0 Incidence Grp2: 0	
Malone, 2003[112] RCT	Grp1: Metformin + glibenclamide Varied; Varied, fasting and pre-meal goal <7mmol/L, 2-hour post-prandial goal <10mmol/L Max: 2550 mg, Mean: 1968 mg; Mean: 14.2 mg D: 4 wks; 16 wks Grp2: Metformin + lispro 75/25 Varied; Varied, fasting and pre-meal goal <7mmol/L, 2-hour post-prandial goal <10mmol/L Max: 2550 mg; Mean: 0.19 U/kg in am and 0.14 U/kg in evening D: 4 wks; 16 wks	Grp1: 0 (0) Grp2: 1 (<1)			
Malone, 2005[205] RCT	Grp1: Metformin + lispro 75/25 Varied, pre-meal glucose 90-126 mg/dL; 2-hr postprandial 144-180 mg/dL Start: 1500 mg, Max: 2550 mg, Mean: 2146 mg; Mean: 0.42 U/kg BID D: 4 wks, 16 wks Grp2: Metformin + glargine	Grp1: 1 (2) Grp2: 1 (2)	Grp1: 1 (2) Grp2: 0 (0)		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Varied, pre-meal glucose 90-126 mg/dL Start: 1500 mg, Max: 2500 mg, Mean: 2146 mg; Mean: 0.36 U/Kg QD D: 4 wks, 16 wks				
Masica, 2013[206] Retrospective cohort	Grp1: Metformin Not specified Grp2: TZD Not specified ITT: Yes Followup (wks): 12 Active			Def:CVD morbidity Unspecified CVD morbidity outcomeincreased blood glucose Incidence Grp1: 0 Incidence Grp2: 0	
Masica, 2013[206] Retrospective cohort	Grp1: Metformin Not specified Grp2: TZD Not specified ITT: Yes Followup (wks): 26 Passive			Def:CVD morbidity Other CVD morbidity (discontinuation due to hypertensive heart disease. Discontinuation because of serious adverse event.) Incidence Grp1: Incidence Grp2:	
Masica, 2013[206] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 26 Passive			Def:CVD morbidity Other CVD morbidity (discontinuation due to hypertensive heart disease. Discontinuation because of serious adverse event.) Incidence Grp1: Incidence Grp2: 1	
Masica, 2013[206] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 12			Def:CVD morbidity Other CVD morbidity (CEC-confirmed cardiovascular event - ST elevation myocardial infarction)	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
				Incidence Grp1: Incidence Grp2: 1	
Masica, 2013[206] Retrospective cohort	Grp1: SU Not specified Grp2: TZD Not specified ITT: Yes Followup (wks): 12			Def:CVD morbidity Other CVD morbidity (acute MI) Incidence Grp1: 0 Incidence Grp2: 2	
Masica, 2013[206] Retrospective cohort	Grp1: SU Not specified Grp2: TZD Not specified ITT: No Followup (wks): 12 NR/unclear			Def:CVD morbidity Other CVD morbidity (Prinzmetal angina) Incidence Grp1: 1 Incidence Grp2:	
Mogensen, 2014[207] Retrospective cohort	Grp1: Metformin + glp-1 agonist Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: No Followup (wks): 12 NR/unclear			Def:CVD morbidity Other CVD morbidity (Prinzmetal angina) Incidence Grp1: 1 Incidence Grp2:	
Mogensen, 2014[207] Retrospective cohort	Grp1: Metformin + glp-1 agonist Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: No Followup (wks): 48			Def:CVD morbidity Nonfatal MI (no definition) Incidence Grp1: 0 Incidence Grp2: 0	
Mogensen, 2014[207]	Grp1: Metformin + su			Def:CVD morbidity	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Retrospective cohort	Not specified Not specified Grp2: Metformin + glp-1 agonist Not specified Not specified ITT: Yes Followup (wks): Active			Nonfatal MI (non ST segment myocardial infarction with pulmonary edema and stent placed) Incidence Grp1: Incidence Grp2: 1	
Mogensen, 2014[207] Retrospective cohort	Grp1: Metformin + su Not specified Not specified Grp2: Metformin + glp-1 agonist Not specified Not specified ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (ICD9 410-413, 414-414.05, 414.8, 414.9, 428.9, 430-438, 440-448 (Except 440 and 440.1)) Incidence Grp1: 2241 Person-years p NR RH 0.31 Incidence Grp2: 1017 Person-years p NR RH ref	
Mogensen, 2014[207] Retrospective cohort	Grp1: Metformin + su Not specified Not specified Grp2: Metformin + dpp-4 inhibitor Not specified Not specified ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (ICD9 410-413, 414-414.05, 414.8, 414.9, 428.9, 430-438, 440-448 (Except 440 and 440.1)) Incidence Grp1: 2241 Person-years p NR RH 0.31 Incidence Grp2: 745 Person-years p NR RH 0.52	
Mogensen, 2014[207] Retrospective	Grp1: Metformin + su Not specified			Def:CVD morbidity Nonfatal MI	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
cohort	Not specified Grp2: Metformin + dpp-4 inhibitor Not specified Not specified ITT: Yes Followup (wks): 16 NR/unclear			(Discontinuation due to myocardial ischemia - did not specify as fatal or nonfatal) Incidence Grp1: 1 Incidence Grp2:	
Mogensen, 2014[207] Retrospective cohort	Grp1: Metformin + su Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: No Followup (wks): 58			Def:CVD morbidity CVD morbidity composite outcome (vascular events) Incidence Grp1: 11 Incidence Grp2: 8	
Mogensen, 2014[207] Retrospective cohort	Grp1: Metformin + su Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: No Followup (wks): 58			Def:CVD morbidity CVD morbidity composite outcome (vascular event) Incidence Grp1: 100 Person-years p NR Incidence Grp2: 100 Person-years p NR	
Mogensen, 2014[207] Retrospective cohort	Grp1: Metformin + dpp-4 inhibitor Not specified Not specified Grp2: Metformin + glp-1 agonist Not specified Not specified ITT: Yes Followup (wks): 144			Def:CVD morbidity CVD morbidity composite outcome (including nonfatal myocardial infarction, nonfatal stroke, or arterial revascularization by PTCA or by coronary artery bypass graft, death from a	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
				cardiovascular cause, and death from any cause, obtained and confirmed by th Incidence Grp1: 39 NA p NR RH 0.54 Incidence Grp2: 52 NA p NR RH	
Mogensen, 2014[207] Retrospective cohort	Grp1: Metformin + dpp-4 inhibitor Not specified Not specified Grp2: Metformin + glp-1 agonist Not specified Not specified ITT: Yes Followup (wks): 144 Active			Def:CVD morbidity Other CVD morbidity (new peripheral vascular disease events not further specified but confirmed by medical record) Incidence Grp1: 1 NA p NR RH 0.13 Incidence Grp2: 6 NA p NR RH	
Mogensen, 2014[207] Retrospective cohort	Grp1: Metformin + dpp-4 inhibitor Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: Yes Followup (wks): 144			Def:CVD morbidity Other CVD morbidity (new or worsening angina confirmed by medical record) Incidence Grp1: 77 NA p NR RH 1.07 Incidence Grp2: 71 NA p NR RH	
Mogensen, 2014[207] Retrospective cohort	Grp1: Metformin + dpp-4 inhibitor Not specified Not specified Grp2: Metformin + basal insulin Not specified Not specified ITT: Yes			Def:CVD morbidity Other CVD morbidity (new critical cardiac arrhythmia confirmed by medical record) Incidence Grp1: 30 NA p NR RH 1.01 Incidence Grp2: 27 NA p NR RH	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 144				
Nauck, 2007[118] RCT	Grp1: Metformin + glipizide NR Grp2: Metformin + sitagliptin NR	Grp1: 2 (0.3) Grp2: 1 (0.2)	Def: Fatal MI Grp1: 1 (0.2) Grp2: 0 (0)		
Nauck, 2009[119] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT: Yes Followup (wks): 144			Def:CVD morbidity Nonfatal MI (no specific definition - confirmed by medical records at each institution) Incidence Grp1: 5 Incidence Grp2: 6	
Nauck, 2009[119] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT: Yes Followup (wks): 144			Def:CVD morbidity Other CVD morbidity (arterial revascularization by PTCA or by coronary artery bypass graft confirmed by medical records) Incidence Grp1: 21 Incidence Grp2: 25	
Nauck, 2009[119] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose)			Def:CVD morbidity CVD morbidity composite outcome (AMI and stroke events only) Incidence Grp1: 179351 Person-years p NR RH 1.00 (ref)	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks): 260			Incidence Grp2: 101125 Person-years p NR RH 1.15	
Nauck, 2009[119] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks): 260			Def:CVD morbidity CVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death) Incidence Grp1: 179351 Person-years p NR RH 1.00 (Ref) Incidence Grp2: 101125 Person-years p NR RH 1.21	
Nauck, 2009[119] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death) Incidence p RH 1 Incidence p RH 1.18	
Nauck, 2009[119] RCT	Grp1: Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2: Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or			Def:CVD morbidity CVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death)	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	maximum tolerated dose) Fixed (12.5mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Incidence p RH 1 Incidence p RH 1.28	
Nauck, 2011[120] RCT	Grp1: Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2: Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity Other CVD morbidity Incidence p RH 1 Incidence p RH 1.24	
Nauck, 2011[120] RCT	Grp1: Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2: Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death) Incidence p RH 1 Incidence p RH 1.18	
Nauck, 2014[121] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT: Not applicable (e.g., cohort)			Def:CVD morbidity CVD morbidity composite outcome (diagnosis of myocardial infarction, angina pectoris, intracerebral	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): NR/unclear			haemorrhage, cerebral infarction, unspecified stroke, peripheral vascular disease, or intervention with percutaneous coronary intervention or coronary arte Incidence Grp1: 1734 p RH 1.00 REF Incidence Grp2: 1338 p RH 1.28	
Nauck, 2014[121] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT: No Followup (wks): 25 NR/unclear			Def:CVD morbidity Other CVD morbidity (UNstable angina) Incidence Grp1: 0 p NR Incidence Grp2: 2 p NR	
Nauck, 2014[121] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT: No Followup (wks): 25 NR/unclear			Def:CVD morbidity Other CVD morbidity (carotid artery occlusion) Incidence Grp1: 0 p Incidence Grp2: 1 p	
Nauck, 2014[121] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: No Followup (wks): 25 NR/unclear			Def:CVD morbidity Nonfatal MI (Acute myocardial infarction) Incidence Grp1: 1 Incidence Grp2: 0	
Nauck, 2014[121] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide			Def:CVD morbidity Other CVD morbidity (Angina pectoris)	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Followup (wks): 25 NR/unclear			Incidence Grp1: 1 Persons p NR Incidence Grp2: 1 Persons p NR	
Nauck, 2014[121] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: No Followup (wks): 18 NR/unclear			Def:CVD morbidity Nonfatal MI (Acute cardiovascular event-Myocardial ischemia or MI) Incidence Grp1: 1 Persons p Incidence Grp2: 1 Persons p	
Nauck, 2014[121] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: No Followup (wks): 52 NR/unclear			Def:CVD morbidity Other CVD morbidity (Vascular Disorders') Incidence Grp1: 10 (7.6) p Incidence Grp2: 17 (6.3) p	
Nauck, 2014[121] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: No Followup (wks): 52 NR/unclear			Def:CVD morbidity Other CVD morbidity (Cardiac disorders') Incidence Grp1: 14 (10.6) NA p Incidence Grp2: 17 (6.3) NA p	
Nauck, 2014[121] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Yes Followup (wks): 24			Def:CVD morbidity Other CVD morbidity (defined as 'acute cardiovascuar event') Incidence Grp1: 1 p Incidence Grp2: 1 p	
Nauck, 2014[121]	Grp1: Metformin + sitagliptin			Def:CVD morbidity	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: No Followup (wks): 80 NR/unclear			CVD morbidity composite outcome (ischemic events') Incidence Grp1: 4 (1) p Incidence Grp2: 6 (2) p	
Nauck, 2014[121] RCT	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear			Def:CVD morbidity CVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99)) Incidence Grp1: 1646 p RH 1 Incidence Grp2: 1376 p RH 1.12	
Nauck, 2014[121] RCT	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear			Def:CVD morbidity CVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99)) Incidence Grp1: 245 p RH 1 Incidence Grp2: 267 p RH 1.29	
Nauck, 2014[121] RCT	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg)			Def:CVD morbidity CVD morbidity composite outcome (MI,	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear			Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99)) Incidence Grp1: 1646 p RH 1 Incidence Grp2: 820 p RH 1.17	
Nauck, 2014[121] RCT	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear			Def:CVD morbidity CVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99)) Incidence Grp1: 245 p RH 1 Incidence Grp2: 154 p RH 1.46	
Nauck, 2014[121] RCT	Grp1: Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2: Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear			Def:CVD morbidity CVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99)) Incidence Grp1: 245 p RH 1 Incidence Grp2: 751 p RH 1.29	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Pantalone, 2009[208] Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR	Grp1: ref Grp2: HR: 1.33 (CI: 0.93 to 1.91) p: 0.11		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: ref Grp2: HR: 0.96 (CI: 0.76 to 1.21) p: 0.74	
Pantalone, 2009[208] Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR	Grp1: ref Grp2: HR: 1.08 (CI: 0.78 to 1.51) p: 0.64		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: ref Grp2: HR: 1.11 (CI: 0.91 to 1.34) p: 0.32	
Pantalone, 2009[208] Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR	Grp1: HR: 0.54 (CI: 0.46 to 0.64) p: <0.001 Grp2: ref		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: HR: 0.94 (CI: 0.85 to 1.05) p: 0.23 Grp2: ref	
Pantalone, 2009[208] Cohort	Grp1: Rosiglitazone NR Grp2: Pioglitazone NR	Grp1: ref Grp2: HR: 0.81 (CI: 0.52 to 1.27) p: 0.36		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: ref Grp2: HR: 1.15 (CI: 0.87 to 1.53) p: 0.32	
Pantalone, 2009[208] Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR	Grp1: HR: 0.73 (CI: 0.51 to 1.02) p: 0.08 Grp2: ref		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: HR: 0.90 (CI: 0.71 to 1.14) p: 0.41 Grp2: ref	
Pantalone, 2009[208] Cohort	Grp1: Pioglitazone NR Grp2: Sulfonylurea NR	Grp1: HR: 0.59 (CI: 0.43 to 0.81) p: <0.001 Grp2: ref		Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baseline Grp1: HR: 1.04 (CI: 0.86 to 1.26) p: 0.69 Grp2: ref	
Pantalone, 2012[209] Retrospective cohort	Grp1: Metformin Not specified Grp2: Glipizide			Def:CVD morbidity CVD morbidity composite outcome (MI,	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Not specified ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear			Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99)) Incidence Grp1: 1646 p RH 1 Incidence Grp2: 3517 p RH 1.21	
Pantalone, 2012[209] Retrospective cohort	Grp1: Metformin Not specified Grp2: Glyburide Not specified ITT: No Followup (wks): 24			Def:CVD morbidity CVD morbidity composite outcome (not prespecified as a composite outcome but this is what is reported on - CAD, carotid artery stenosis, peripheral artery disease) Incidence p Incidence p	
Pantalone, 2012[209] Retrospective cohort	Grp1: Metformin Not specified Grp2: Glimepiride Not specified ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity Nonfatal MI (ï¬□rst-time discharge diagnosis of MI) Incidence Grp1: 599 5927 Persons p OR 0.86 Incidence Grp2: 3080 26778 Persons p OR 1 REF	
Petrica, 2009[126] RCT	Grp1: Metformin + rosiglitazone Fixed (1700 mg/day) Fixed (4 mg/day) Grp2: Metformin + glimepiride Fixed (1700 mg/day)			Def:CVD morbidity Other CVD morbidity (acute CVD adverse events (unspecified)) Incidence Grp1: (2.1) Incidence Grp2:	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (4 mg/day) ITT: Yes Followup (wks): 76 NR/unclear				
Petrica, 2009[126] RCT	Grp1: Metformin + rosiglitazone Fixed (1700 mg/day) Fixed (4 mg/day) Grp2: Metformin + glimepiride Fixed (1700 mg/day) Fixed (4 mg/day) ITT: Yes Followup (wks): 76 NR/unclear			Def:CVD morbidity Other CVD morbidity (acute CVD adverse events (unspecified)) Incidence Grp1: (2.1) Incidence Grp2: (0.3)	
Pfutzner, 2011[128] RCT	Grp1: Metformin + pioglitazone Fixed (1700 mg/d) Fixed (30 mg/d) Grp2: Metformin + glimepiride Fixed (1700 mg/d) Fixed (2mg/d) ITT: Yes Followup (wks): 76 NR/unclear			Def:CVD morbidity Other CVD morbidity (acute CVD adverse events (unspecified)) Incidence Grp1: (2.1) Incidence Grp2:	
Pfutzner, 2011[129] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Saxagliptin + placebo Fixed (10 mg) ITT: Yes Followup (wks): 76 NR/unclear			Def:CVD morbidity Other CVD morbidity (acute CVD adverse events (unspecified)) Incidence Grp1: Incidence Grp2: (0.3)	
Pfutzner, 2011[129] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Saxagliptin + placebo Fixed (10 mg) ITT: Yes Followup (wks): 76 NR/unclear			Def:CVD morbidity Other CVD morbidity (acute CVD adverse events (unspecified)) Incidence Grp1: Incidence Grp2:	
Pfutzner, 2011[129]	Grp1: Metformin + placebo			Def:CVD morbidity	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Titrated (Max: 2000 mg) Grp2: Saxagliptin + placebo Fixed (10 mg) ITT: Yes Followup (wks): 104			Nonfatal MI (myocardial infarction, judged to have a possible relationship to trial drug by investigator) Incidence Grp1: 1 Incidence Grp2: 1	
Pfutzner, 2011[129] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Saxagliptin + placebo Fixed (10 mg) ITT: Followup (wks): 104			Def:CVD morbidity Other CVD morbidity (cardiac disorders) Incidence Grp1: 14 (6) Incidence Grp2: 8 (3)	
Pfutzner, 2011[129] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Followup (wks): 104			Def:CVD morbidity Other CVD morbidity (cardiac disorders) Incidence Grp1: 14 (6) Incidence Grp2: 11 (5)	
Pfutzner, 2011[129] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: Yes Followup (wks): 104			Def:CVD morbidity Nonfatal MI (myocardial infarction, judged to have a possible relationship to trial drug by investigator) Incidence Grp1: 1 Incidence Grp2: 1	
Pfutzner, 2011[129] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (death from any cause or first hospitalization for myocardial infarction (ICD-9 code 410-412.99 and 414. xx), cerebrovascular	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
				disease (430â€“437.1 and procedure code 38.12), coronary artery bypass graft (36.10â€“36.16 and 3 Incidence p RH Incidence p RH 1.15	
Pfutzner, 2011[129] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: NR Followup (wks): 104			Def:CVD morbidity CVD morbidity composite outcome (CV AEs (qualitatively reported)) Incidence p Incidence p	
Pfutzner, 2011[129] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 26			Def:CVD morbidity Other CVD morbidity (Unstable Angina) Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p	
Pfutzner, 2011[129] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 26			Def:CVD morbidity Other CVD morbidity (Coronary artery occlusion) Incidence Grp1: 2 (1) Persons p NR Incidence Grp2: 0 (0) Persons p NR	
Pfutzner, 2011[129] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 26			Def:CVD morbidity Other CVD morbidity (Unstable Angina) Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Pfutzner, 2011[129] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 26			Def:CVD morbidity Other CVD morbidity (Coronary artery occlusion) Incidence Grp1: 2 (1) Persons p NR Incidence Grp2: 0 (0) Persons p NR	
Pfutzner, 2011[129] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: No Followup (wks): 26			Def:CVD morbidity Other CVD morbidity (Unstable Angina) Incidence Grp1: 0 (0) Persons p Incidence Grp2: 0 (0) Persons p	
Pfutzner, 2011[129] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: No Followup (wks): 26			Def:CVD morbidity Other CVD morbidity (Coronary artery occlusion) Incidence Grp1: 0 (0) Persons p NR Incidence Grp2: 0 (0) Persons p NR	
Pfutzner, 2011[129] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Not applicable (e.g., cohort) Followup (wks):			Def:CVD morbidity CVD morbidity composite outcome (all-cause mortality, AMI and stroke) Incidence Grp1: 4286 (5.1) p RR REF Incidence Grp2: 62 (5) p RR 1.22	
Pfutzner, 2011[129] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: Yes		Def:CVD mortality Other CVD mortality (cardiopulmonary arrest and myocardial infarction) Incidence Grp1:		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 102		Incidence Grp2: 2		
Pfutzner, 2011[129] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 102		Def:CVD mortality Other CVD mortality (cardiopulmonary arrest and myocardial infarction) Incidence Grp1: Incidence Grp2:		
Pfutzner, 2011[129] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: Yes Followup (wks): 102		Def:CVD mortality Other CVD mortality (cardiopulmonary arrest and myocardial infarction) Incidence Grp1: Incidence Grp2:		
Pfutzner, 2011[129] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT: Yes Followup (wks): 52 Active		Def:CVD mortality Fatal MI Incidence Grp1: 0 Incidence Grp2: 1		
Pfutzner, 2011[129] RCT	Grp1: Saxagliptin + placebo Fixed (10 mg) Grp2: Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT: Yes Followup (wks): 104		Def:CVD mortality Composite CVD mortality outcome (sudden cardiac death, fatal myocardial infarction, and fatal stroke) Incidence Grp1: 2 NA p NR RR Incidence Grp2: 2 NA p NR RR 1		
Pratley, 2010[130] RCT	Grp1: Metformin + sitagliptin NS; Max: 100 mg		Def: Fatal cardiac arrest		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + liraglutide Varied, HgbA1c: 7.5-10% NS; Start: 0.6 mg, Max: 1.8 mg		Grp1: 1 (<1) Grp2: 0 (0)		
Pratley, 2010[130] RCT	Grp1: Metformin + sitagliptin NS; Max: 100 mg Grp2: Metformin + liraglutide Varied, HgbA1c: 7.5-10% NS; Start: 0.6 mg, Max: 1.2 mg		Def: Fatal cardiac arrest Grp1: 1 (<1) Grp2: 0 (0)		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2: 1		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[131]	Grp1: Metformin		Def:CVD mortality		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: 1 Incidence Grp2:		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (2000 mg)		Def:CVD mortality Other CVD mortality		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: No Followup (wks): 26 NR/unclear		(sudden cardiac death) Incidence Grp1: 1 Incidence Grp2:		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: No Followup (wks): 26 NR/unclear		Def:CVD mortality Other CVD mortality (sudden cardiac death) Incidence Grp1: Incidence Grp2:		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 0 Incidence Grp2: 0		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 1 Incidence Grp2: 0		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 1 Incidence Grp2: 0		
Pratley, 2014[131]	Grp1: Metformin		Def:CVD mortality		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Fatal MI Incidence Grp1: 0 Incidence Grp2: 0		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 0 Incidence Grp2: 0		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (2000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 1 Incidence Grp2: 0		
Pratley, 2014[131] RCT	Grp1: Metformin Fixed (1000 mg) Grp2: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 0 Incidence Grp2: 0		
Pratley, 2014[131] RCT	Grp1: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 24		Def:CVD mortality Fatal MI Incidence Grp1: 0 Incidence Grp2: 0		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Pratley, 2014[131] RCT	Grp1: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 104		Def:CVD mortality Fatal MI Incidence Grp1: 1 408 Persons p NR Incidence Grp2: 0 406 Persons p NR		
Pratley, 2014[131] RCT	Grp1: Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Yes Followup (wks): 12		Def:CVD mortality Other CVD mortality (no fatal adverse events were reported) Incidence Grp1: 0 Incidence Grp2: 0		
Pratley, 2014[131] RCT	Grp1: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Not applicable (e.g., cohort) Followup (wks):		Def:CVD mortality Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 10 3246 Person-years p Rate ratio (poisson) 0.89 Incidence Grp2: 91 6916 Person-years p Rate ratio (poisson) 1.57		
Pratley, 2014[131] RCT	Grp1: Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Not applicable (e.g., cohort) Followup (wks):		Def:CVD mortality Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 256 31497 Person-years p Rate ratio (poisson) 1 (Ref) Incidence Grp2: 10 3246 Person-years p Rate ratio (poisson) 0.89		
Pratley, 2014[131]	Grp1: Metformin + alogliptin		Def:CVD mortality		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT: Not applicable (e.g., cohort) Followup (wks):		Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 256 31497 Person-years p Rate ratio (poisson) 1 (Ref) Incidence Grp2: 38 11619 Person-years p Rate ratio (poisson) 0.57		
Qiu, 2014[132] RCT	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin + canagliflozin Fixed (Mean: 2137mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (50mg BID) ITT: Not applicable (e.g., cohort) Followup (wks):		Def:CVD mortality Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 256 31497 Person-years p Rate ratio (poisson) 1 (Ref) Incidence Grp2: 91 6916 Person-years p Rate ratio (poisson) 1.57		
Qiu, 2014[132] RCT	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin + canagliflozin Fixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to		Def:CVD mortality Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 38 11619 Person-years p Rate ratio (poisson) 0.57 Incidence Grp2: 10 3246 Person-years p Rate ratio (poisson) 0.89		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	tolerate a higher dose) for >= 8 wks prior to screening) Fixed (150mg BID) ITT: Not applicable (e.g., cohort) Followup (wks):				
Qiu, 2014[132] RCT	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin + canagliflozin Fixed (Mean: 2137mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (50mg BID) ITT: Not applicable (e.g., cohort) Followup (wks):		Def:CVD mortality Other CVD mortality (ICD-10: I00-I99) Incidence Grp1: 38 11619 Person-years p Rate ratio (poisson) 0.57 Incidence Grp2: 91 6916 Person-years p Rate ratio (poisson) 1.57		
Qiu, 2014[132] RCT	Grp1: Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2: Metformin + canagliflozin Fixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (150mg BID)		Def:CVD mortality Unspecified CVD mortality Incidence Grp1: 0 Incidence Grp2: 0		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: No Followup (wks): 48				
Raz, 2008[188] RCT	Grp1: Metformin Fixed Grp2: Metformin + sitagliptin Fixed Max: 2550 mg; Mean: 100 mg	Grp1: 1 (1) Grp2: 0 (0)	Def: Fatal MI Grp1: 1 (1) Grp2: 0 (0)		
Reasner, 2011[135] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 58		Def:CVD mortality Fatal MI Incidence Grp1: 2 Incidence Grp2:		
Reasner, 2011[135] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: Yes Followup (wks): 144		Def:CVD mortality Other CVD mortality (not specified but confirmed by medical record and death certificates at each institution) Incidence Grp1: 7 Incidence Grp2: 11		
Ridderstrale, 2014[136] RCT	Grp1: Metformin + glimepiride Fixed (Mean: 2.71 mg/day (mean max titrated dose of glimep(ГëÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Titrated (Max: 4mg) Grp2: Metformin + empagliflozin Fixed ((ГëÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label)		Def:CVD mortality Composite CVD mortality outcome (death within 28 days of CVD was defined as diagnosis of myocardial infarction (ICD â€□ 10 code I21), angina pectoris (ICD â€□ 10 code I20.0), intracerebral haemorrhage, cerebral infarction, unspecified		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		stroke (ICD â€□ 10 c Incidence Grp1: 264 NA p NR RH 1.00 REF Incidence Grp2: 276 NA p NR RH Non-Proportional hazard, excluded from analysis		
Ridderstrale, 2014[136] RCT	Grp1: Metformin + glimepiride Fixed (Mean: 2.71 mg/day (mean max titrated dose of glimep(ГёÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Titrated (Max: 4mg) Grp2: Metformin + empagliflozin Fixed ((ГёÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Fixed (25mg) ITT: No Followup (wks): 80 NR/unclear		Def:CVD mortality Other CVD mortality (fata MI) Incidence p Incidence p		
Rigby, 2009[137] RCT	Grp1: Metformin + rosiglitazone Fixed NS; Mean: 4 mg Grp2: Metformin + sitagliptin NS: Mean: 100 mg			Def: Transient ischemic cerebrovascular accident Grp1: 1 (2) Grp2: 0 (0)	
Roden, 2013[139] RCT	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (10 mg) ITT: Not applicable (e.g.,		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99)) Incidence Grp1:		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	cohort) Followup (wks): NR/unclear		169 p RH 1 Incidence Grp2: 207 p RH 1.5		
Roden, 2013[139] RCT	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (25 mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99)) Incidence Grp1: 827 p RH 1 Incidence Grp2: 876 p RH 1.14		
Roden, 2013[139] RCT	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (10 mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99)) Incidence Grp1: 827 p RH 1 Incidence Grp2: 559 p RH 1.25		
Roden, 2013[139] RCT	Grp1: Sitagliptin Fixed (100 mg) Grp2: Empagliflozin Fixed (25 mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99)) Incidence Grp1: 169 p RH 1 Incidence Grp2: 115 p RH 1.63		
Rosenstock, 2006[140] RCT	Grp1: Metformin Varied, glucose: 6.1 mmol/l Start: 500 mg, Mean: 1847 mg, Max: 2000 mg D: 32 wks Grp2: Rosiglitazone Varied, glucose: 6.1 mmol/l Start: 4 mg, Mean: 7.7 mg, Max: 8 mg D: 32 wks	Grp1: 0 (0) Grp2: 0 (0)		Def: Not defined ischemic heart disease Grp1: 2 (1) Grp2: 2 (1)	
Rosenstock, 2006[140]	Grp1: Metformin Varied, glucose: 6.1 mmol/l	Grp1: 0 (0) Grp2: 0 (0)		Def: Not defined ischemic heart disease	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Metformin + rosiglitazone Varied, glucose: 6.1 mmol/l Start: 500 mg, Mean: 1799 mg, Max: 2000 mg; Start: 2 mg, Max: 8 mg, Mean: 7.2mg D: 32 wks			Grp1: 2 (1) Grp2: 1 (1)	
Rosenstock, 2013[144] RCT	Grp1: Metformin + placebo Not specified (prestudy dose: Γëѐ1500 mg/day or maximum tolerated dose) Grp2: Metformin + sitagliptin Not specified (prestud dose: Γëѐ1500 mg/day or maximum tolerated dose) Fixed (100mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99)) Incidence Grp1: 827 p RH 1 Incidence Grp2: 2251 p RH 1.28		
Rosenstock, 2013[144] RCT	Grp1: Metformin + placebo Not specified (prestudy dose: Γëѐ1500 mg/day or maximum tolerated dose) Grp2: Metformin + empagliflozin Not specified (prestudy dose: Γëѐ1500 mg/day or maximum tolerated dose) Fixed (10mg) ITT: Not applicable (e.g., cohort) Followup (wks): NR/unclear		Def:CVD mortality Other CVD mortality (cardiovascular death (ICD-10 I00 â€“I99)) Incidence Grp1: 169 p RH 1 Incidence Grp2: 591 p RH 1.32		
Rosenstock, 2013[144]	Grp1: Metformin + placebo Not specified (prestudy dose:		Def:CVD mortality Composite CVD		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
RCT	ГëÑ1500 mg/day or maximum tolerated dose) Grp2: Metformin + empagliflozin Not specified (prestudy dose: ГëÑ1500 mg/day or maximum tolerated dose) Fixed (25mg) ITT: Yes Followup (wks): 44		mortality outcome (fatal acute myocardial infarction and cario-respiratory arrest) Incidence Grp1: 1 Incidence Grp2: 1		
Rosenstock, 2013[144] RCT	Grp1: Metformin + sitagliptin Not specified (prestud dose: ГëÑ1500 mg/day or maximum tolerated dose) Fixed (100mg) Grp2: Metformin + empagliflozin Not specified (prestudy dose: ГëÑ1500 mg/day or maximum tolerated dose) Fixed (10mg) ITT: Yes Followup (wks): 76		Def:CVD mortality Other CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI) Incidence Grp1: 3 Incidence Grp2: 1		
Rosenstock, 2013[144] RCT	Grp1: Metformin + sitagliptin Not specified (prestud dose: ГëÑ1500 mg/day or maximum tolerated dose) Fixed (100mg) Grp2: Metformin + empagliflozin Not specified (prestudy dose: ГëÑ1500 mg/day or maximum tolerated dose) Fixed (25mg) ITT: Yes Followup (wks): 76		Def:CVD mortality Other CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI) Incidence Grp1: 3 Incidence Grp2: 0		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Ross, 2012[146] RCT	Grp1: Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2: Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT: Yes Followup (wks): 76		Def:CVD mortality Other CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI) Incidence Grp1: 3 Incidence Grp2: 2		
Ross, 2012[146] RCT	Grp1: Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2: Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT: Yes Followup (wks): 76		Def:CVD mortality Other CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI) Incidence Grp1: 1 Incidence Grp2: 0		
Ross, 2012[146] RCT	Grp1: Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2: Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT: Yes Followup (wks): 76		Def:CVD mortality Other CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI) Incidence Grp1: 1 Incidence Grp2: 2		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
Ross, 2012[146] RCT	Grp1: Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2: Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT: Yes Followup (wks): 104		Def:CVD mortality Composite CVD mortality outcome (cardiac failure, myocardial infarction) Incidence Grp1: 1 Incidence Grp2: 1		
Roumie, 2012[210] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Not applicable (e.g., cohort) Followup (wks):		Def:CVD mortality Other CVD mortality (death from cardiovascular causes (ICD- 10 codes I00â€“I99)) Incidence Grp1: 109 1533 Person-years p 0.79 Incidence Grp2: 1378 9570 Person-years p 1 REF		
Roumie, 2012[210] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Not applicable (e.g., cohort) Followup (wks):		Def:CVD mortality Other CVD mortality (death from cardiovascular causes (ICD- 10 codes I00â€“I99)) Incidence Grp1: 109 1533 Person-years p 0.79 Incidence Grp2: 447 4280 Person-years p 0.94		
Roumie, 2012[210] Retrospective	Grp1: Metformin Not specified		Def:CVD mortality Other CVD mortality		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
cohort	Grp2: SU Not specified ITT: Not applicable (e.g., cohort) Followup (wks):		(death from cardiovascular causes (ICD- 10 codes I00â€“I99)) Incidence Grp1: 1378 9570 Person-years p 1 REF Incidence Grp2: 447 4280 Person-years p 0.94		
Roumie, 2012[210] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2:		
Roumie, 2012[210] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2:		
Roumie, 2012[210] Retrospective cohort	Grp1: Metformin Not specified Grp2: SU Not specified ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: 1 Incidence Grp2:		
Russell-Jones, 2012[147] RCT	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) ITT: Yes		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2: 1		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	Followup (wks): 104				
Russell-Jones, 2012[147] RCT	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: 1 Incidence Grp2: 1		
Russell-Jones, 2012[147] RCT	Grp1: Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2: Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2: 1		
Russell-Jones, 2012[147] RCT	Grp1: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2: Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2:		
Russell-Jones, 2012[147] RCT	Grp1: Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2: Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW)		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2:		

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	ITT: Yes Followup (wks): 104				
Russell-Jones, 2012[147] RCT	Grp1: Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) Grp2: Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: 1 Incidence Grp2:		
Scheller, 2014[211] Retrospective cohort	Grp1: Metformin Not specified Grp2: Sitagliptin Not specified ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2: 1		
Scheller, 2014[211] Retrospective cohort	Grp1: Metformin Not specified Grp2: Sitagliptin Not specified ITT: Yes Followup (wks): 104		Def:CVD mortality Other CVD mortality (sudden cardiac death or worsening CAD) Incidence Grp1: Incidence Grp2:		
Schernthaner, 2015[148]	Grp1: Metformin + glimepiride + placebo Mean: 1572 mg/d Titrated (Mean: 3.3 mg/d Max: 6mg/d) Grp2: Metformin + saxagliptin + placebo Mean: 1647 Fixed (5 mg/d) ITT: No Followup (wks): 52	Def: All-cause mortality Incidence Grp1: 1 Incidence Grp2: 1	Fatal MI Incidence Grp1: NR Incidence Grp2: 1		
Schernthaner,	Grp1: Metformin	Grp1: 2 (0.3)			

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
2004[149] RCT	Varied Max: 850 mg tid Grp2: Pioglitazone Varied Start: 30 mg, Max: 45 mg	Grp2: 3 (0.5)			
Schumm-Draeger, 2015[151]	Grp1: Metformin + placebo Fixed (adjusted to 1500, 2000, 2500 mg/d) Grp2: Metformin + dapagliflozin Fixed 5 mg twice daily	Grp1: 0 (0) Grp2: 0 (0)			
Schumm-Draeger, 2015[151]	Grp1: Metformin + placebo Fixed (adjusted to 1500, 2000, 2500 mg/d) Grp2: Metformin + dapagliflozin Fixed 10 mg/d	Grp1: 0 (0) Grp2: 0 (0)			
Seck, 2010[154] RCT	Grp1: Metformin + sitagliptin Fixed Grp2: Metformin + glipizide Fixed; Varied, glucose > 110 mg/dl NR; Start: 5 mg, Max: 20 mg, Mean: 9.2 mg	Grp1: 8 (1.4) Grp2: 1 (0.2)	Def: Sudden cardiac death Grp1: 2 (<1) Grp2: 0 (0)		
St John Sutton, 2002[159] RCT	Grp1: Rosiglitazone Fixed Start: 4 mg bid Grp2: Glyburide Varied Max: 20 mg			Def: CVD morbidity/heart disease Grp1: 9 (9) Grp2: 5 (5)	
Stewart, 2006[160] RCT	Grp1: Metformin Varied Start: 500 mg, Mean: 2627.9 mg, Max: 3000 mg D: 20wks Grp2: Metformin + rosiglitazone Varied Start: 500 mg, Mean: 1812.9			Def: MI, angina pectoris, myocardial ischemic, coronary artery insufficiency Grp1: 0 (0) Grp2: 4 (2)	

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
	mg, Max: 2000 mg D: 18 wks				
van der Meer, 2009[172] RCT	Grp1: Metformin + glimepiride Fixed Start: 1000 mg, Max: 2000 mg; Start: 15 mg, Max: 30 mg D: 8 wks Grp2: Pioglitazone + glimepiride Varied Not specified D: 8 wks		Def: CVD event Grp1: 0 (0) Grp2: 0 (0)		
Wang, 2015[173] RCT	Grp1: Metformin + placebo Fixed >=1500 mg/day or maximum tolerated dose Grp2: Metformin + lingliptin Fixed >=1500 mg/day or max tolerated dose Fixed 5mg			Nonfatal MI (suspected Myocardial Ischemia) Incidence Grp1: 0 Incidence Grp2: 1	Nonfatal stroke (lacunar infarction) Incidence Grp1: 1 Incidence Grp2: 0
Weissman, 2005[174] RCT	Grp1: Metformin Varied Start: 1000mg, Max: 2000mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 1000 mg; Start: 4 mg, Max: 8 mg	Grp1: 0 (0) Grp2: 1 (<1)		Def: CVD morbidity/MI (non-fatal) Grp1: 0 (0) Grp2: 2 (1)	
Weissman, 2005[174] RCT	Grp1: Metformin Varied Start: 1000mg, Max: 2000mg Grp2: Metformin + rosiglitazone Fixed; Varied Start: 1000 mg; Start: 4 mg, Max: 8 mg			Def: CVD morbidity/MI (non-fatal) + pulmonary edema with MI Grp1: 3 + 1 withdrew (1) Grp2: 5 (1)	
Xu, 2015[178]	Grp1: Pioglitazone Titrated 45 mg/d Grp2: Exenatide Titrated 10ug twice daily				Def: Other cerebrovascular (cerebral infarction) Grp1:NR(1)

Author, year Study design	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Cerebrovascular disease, n (%)
					Grp2: NR(1)

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not Reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table D8. Results of studies evaluating effects of diabetes medications on nephropathy and neuropathy

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified ITT: Yes Followup (wks): 52, Active	Def:Nephropathy Nephropathy defined as (Renal adverse event) Incidence Grp1: (0.6) Incidence Grp2: (0)	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified ITT: Yes Followup (wks): 52, Active	Def:Nephropathy Nephropathy defined as (Renal adverse event) Incidence Grp1: (0.6) Incidence Grp2: (0.6)	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified ITT: No Followup (wks): 12, NR/unclear	Def:Nephropathy Nephropathy defined as (diabetic nephropathy) Incidence Grp1: (1.3) Incidence Grp2: (2.5)	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified ITT: No Followup (wks): 12, Active	Def:Nephropathy Nephropathy defined as (microalbuminuria) Incidence Grp1: (1.3) Incidence Grp2: (3.7)	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glipizide, Not specified ITT: No Followup (wks): 12, Active	Def:Nephropathy Nephropathy defined as (microalbuminuria) Incidence Grp1: (1.3) Incidence Grp2: (0)	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glimepiride, Not specified ITT: No Followup (wks): 12, NR/unclear	Def:Nephropathy Nephropathy defined as (diabetic nephropathy) Incidence Grp1: (1.3) Incidence Grp2: (1.2)	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glimepiride, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH 0.86 Incidence p RH Ref	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (GFR event or ESRD) Incidence p RH 0.78 Incidence p RH ref	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glibenclamide, Not specified	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH 0.85 Incidence p RH Ref	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glipizide, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH 0.85 Incidence p RH 1.01	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glipizide, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH 0.86 Incidence p RH 1.04	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glimepiride, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (GFR event or ESRD) Incidence p RH 0.78 Incidence p RH 1.11	
Schramm, 2011[212] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glimepiride, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH Ref Incidence p RH 1.04	
Seino, 2012[156] RCT	Grp1: Metformin + placebo Fixed (500mg/day, or 750mg/day) Grp2: Metformin + alogliptin Fixed (500mg/day, or 750mg/day) Fixed (12.5mg)	Def:Nephropathy Nephropathy defined as (GFR event or ESRD) Incidence p RH ref Incidence p RH 1.11	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive		
Seino, 2012[156] RCT	Grp1: Metformin + placebo Fixed (500mg/day, or 750mg/day) Grp2: Metformin + alogliptin Fixed (500mg/day, or 750mg/day) Fixed (25mg) ITT: Not applicable (e.g., cohort) Followup (wks): 260, Passive	Def:Nephropathy Nephropathy defined as (composite of GFR event (GFR event was defined as a persistent 25% or greater decline from the baseline eGFR) or ESRD (eGFR <15 mL/minute/1.73m2 or the first inpatient or outpatient code for dialysis or related procedures or renal t Incidence p RH Ref Incidence p RH 1.01	
Stenlof, 2014[213] RCT	Grp1: Sitagliptin Fixed (100mg) Grp2: Canagliflozin Fixed (100mg) ITT: Not applicable (e.g., cohort) Followup (wks): Passive	Def:Nephropathy Nephropathy defined as (renal function decline endpoint was reached if a patient with an eGFR â‰¥60 ml/min/1.73m2 at first measurement had an ensuing eGFR that was <60 ml/min/1.73m2 during follow-up) Incidence p RH 1.00 (ref) Incidence p RH 1.04	
Stenlof, 2014[213] RCT	Grp1: Sitagliptin Fixed (100mg) Grp2: Canagliflozin Fixed (300mg) ITT: Not applicable (e.g., cohort) Followup (wks): Passive	Def:Nephropathy Nephropathy defined as (proteinuria: defined as microalbuminuria or worse), we required that patients have a negative urine protein test at first urine measurement following T2D diagnosis that subsequently became positive during follow-up. Positive test d Incidence p RH 1.00 (ref) Incidence p RH 1	
Suzuki, 2014[161]	Grp1: Sitagliptin Fixed 50 mg/d Grp2: Liraglutide Titrated 0.9 mg/d ITT: No Followup (wks): 24	Def: Nephropathy defined as (Urinary Albumin excretion (ug/g Cr)) Incidence NR	
Suzuki, 2014[161]	Grp1: Sitagliptin Fixed 50 mg/d Grp2: Liraglutide Titrated 0.9 mg/d ITT: No Followup (wks): 24	Def: Nephropathy defined as (Change in eGFR) Incidence NR	
Umpierrez, 2014[171] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up	Def:Nephropathy Nephropathy defined as (proteinuria: defined as	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2: Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 0.75mg) ITT: Not applicable (e.g., cohort) Followup (wks): Passive	microalbuminuria or worse), we required that patients have a negative urine protein test at first urine measurement following T2D diagnosis that subsequently became positive during follow-up. Positive test d Incidence p RH 1.00 (ref) Incidence p RH 1.27	
Umpierrez, 2014[171] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2: Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 1.5mg) ITT: Not applicable (e.g., cohort) Followup (wks): Passive	Def:Nephropathy Nephropathy defined as (renal function decline endpoint was reached if a patient with an eGFR â‰¥60 ml/min/1.73m2 at first measurement had an ensuing eGFR that was <60 ml/min/1.73m2 during follow-up) Incidence p RH 1.00 (ref) Incidence p RH 1.41	
Wheeler, 2013[214] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Rosiglitazone, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): Passive	Def:Nephropathy Nephropathy defined as (renal function decline endpoint was reached if a patient with an eGFR â‰¥60 ml/min/1.73m2 at first measurement had an ensuing eGFR that was <60 ml/min/1.73m2 during follow-up) Incidence p RH 1.41 Incidence p RH 1.04	
Wheeler, 2013[214] Retrospective cohort	Grp1: Metformin, Not specified Grp2: Glipizide, Not specified ITT: Not applicable (e.g., cohort) Followup (wks): Passive	Def:Nephropathy Nephropathy defined as (proteinuria: defined as microalbuminuria or worse), we required that patients have a negative urine protein test at first urine measurement following T2D diagnosis that subsequently became positive during follow-up. Positive test d Incidence p RH 1.27 Incidence p RH 1	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence Grp1: 77420 Person-years p NR RH ref Incidence Grp2: 2014 Person-years p NR RH 0.92	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Sitagliptin + placebo	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH ref Incidence p RH 1.21	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence Grp1: 77420 Person-years p NR RH ref Incidence Grp2: 36592 Person-years p NR RH 1.2	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Sitagliptin + placebo Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p ref Incidence p 1.19	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH ref Incidence p RH 1.21	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH ref Incidence p RH 1.18	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH 1.21 Incidence p RH	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH 1.18 Incidence p RH	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p 1.19 Incidence p	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence Grp1: 36592 Person-years p NR RH 1.2 Incidence Grp2: 2014 Person-years p NR RH 0.92	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Not applicable (e.g., cohort) Followup (wks):	Def:Nephropathy Nephropathy defined as (composite of GFR event (persistent 25% or greater decline from baseline eGFR) and ESRD (eGFR<15 or first inpt or outpt code for dialysis or related procedures or renal transplant)) Incidence p RH 1.21 Incidence p RH	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Yes Followup (wks): 104	Def:Nephropathy Nephropathy defined as (renal and urinary disorders) Incidence Grp1: 15 (6) Incidence Grp2: 13 (5)	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg)	Def:Nephropathy Nephropathy defined as (renal and urinary disorders)	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Yes Followup (wks): 104	Incidence Grp1: 15 (6) Incidence Grp2: 11 (5)	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 26	Def:Nephropathy Nephropathy defined as (Change in albumin to creatinine ratio (%)) Incidence p Incidence p	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 1000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 26	Def:Nephropathy Nephropathy defined as (Change in albumin to creatinine ratio (%)) Incidence p Incidence p	
Williams-Herman, 2010[177] RCT	Grp1: Metformin + placebo Titrated (Max: 2000 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 26	Def:Nephropathy Nephropathy defined as (Change in albumin to creatinine ratio (%)) Incidence p Incidence p	
Williams-Herman, 2010[177] RCT	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: No Followup (wks): 48	Def:Nephropathy Nephropathy defined as (GFR (ml/min per 1.73 m2)) Incidence p Incidence p	
Williams-Herman, 2010[177] RCT	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: No	Def:Nephropathy Nephropathy defined as (urine albumin/creatine (mg/g)) Incidence p Incidence p	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	Followup (wks): 48		
Williams-Herman, 2010[177] RCT	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT: Yes Followup (wks): 26, Passive	Def:Neuropathy Unspecified neuropathy Incidence p Incidence Grp2: 1 p	
Williams-Herman, 2010[177] RCT	Grp1: Sitagliptin + placebo Titrated (Max: 100 mg) Grp2: Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT: Yes Followup (wks): 26, Passive	Def:Neuropathy Unspecified neuropathy Incidence p Incidence Grp2: 1 p	
Yang, 2011[180] RCT	Grp1: Metformin + placebo Fixed (Mean: 1606 mg/dcontd pre-study dose: 1500 - 3000 mg/d) Grp2: Metformin + saxagliptin Fixed (Mean: 1620 mg/dcontd on prestudy dose - 1500 - 3000 mg/d) Fixed (5 mg/d) ITT: Yes Followup (wks): 12, NR/unclear	Def:Retinopathy Unspecified retinopathy Incidence Grp1: 1 Incidence Grp2: 1	
Yang, 2011[180] RCT	Grp1: Metformin + placebo Fixed (Mean: 1606 mg/dcontd pre-study dose: 1500 - 3000 mg/d) Grp2: Metformin + saxagliptin Fixed (Mean: 1620 mg/dcontd on prestudy dose - 1500 - 3000 mg/d) Fixed (5 mg/d) ITT: Yes Followup (wks): 12, NR/unclear	Def:Retinopathy Unspecified retinopathy Incidence Grp1: 1 Incidence Grp2: 0	
Yang, 2012[182] RCT	Grp1: Metformin + placebo Fixed (1000 or 1700 mg/d) Grp2: Metformin + sitagliptin Fixed (1000 or 1700 mg/d) Fixed (100 mg/d) ITT: Yes	Def:Retinopathy Unspecified retinopathy Incidence Grp1: 1 Incidence Grp2: 0	

Author, year Study design	Intervention	Nephropathy, n (%)	Neuropathy, n (%)
	Followup (wks): 12		
Zhang, 2012[187] RCT	Grp1: Metformin + glimepiride Fixed (1.0-1.5g, adjusted in accordance with the levels of blood glucose) Fixed (1-4mg, adjusted in accordance with the levels of blood glucose) Grp2: Metformin + exenatide Fixed (1.0-1.5g, adjusted in accordance with the levels of blood glucose) Fixed (initiated at 10ug for the first 4 wks, 20ug in the subsequent 12 wks then went into 16 week treatment period) ITT: No Followup (wks): 52, Active	Def:Retinopathy Retinopathy defined as (Diabetic retinopathy) Incidence Grp1: 9 (6.8) Incidence Grp2: 16 (6)	

g/day = grams per day; g/dl = grams per deciliter; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not Reported; pmol/l = picomoles per liter; SU = sulfonylurea; TZD = thiazolidinedione; U/kg = units per kilogram; yrs = years

Some data may have not been extracted because the question was not asked.

Table D9. Quality of studies evaluating long-term clinical outcomes

Author, year	Randomized	Randomization Scheme	Double-Blind	Blinding Method	Dropouts Description
Ahren, 2014[2]	Yes	Not described	Yes	Yes	Yes
Alba, 2013[3]	Yes	Yes	Yes	Not described	Yes
Arechavaleta, 2011[5]	Yes	Yes	Yes	Not described	Yes
Arjona Ferreira, 2013[6]	Yes	Yes	Yes	Yes	Yes
Aschner, 2012[8]	Yes	Yes	No	Not described	Yes
Bailey, 2013[10]	Yes	Yes	Yes	Yes	Yes
Barnett, 2012[13]	Yes	Yes	Yes	Yes	Yes
Bergenstal, 2010[14]	Yes	Yes	Yes	Yes	Yes
Bolinder, 2012[17]	Yes	Yes	Yes	Yes	Yes
Borges, 2011[18]	Yes	Not described	Yes	Not described	No
Cefalu, 2013[20]	Yes	Yes	Yes	Yes	Yes
DeFronzo, 2012[31]	Yes	Not described	Yes	Yes	No
Del Prato, 2015[32]	Yes	Not described	Yes	Not described	No
Del Prato, 2014[33]	Yes	Not described	Yes	Yes	Yes
Diamant, 2010[44]	Yes	Yes	No	Not described	Yes
Erem, 2014[47]	Yes	Not described	No	Not described	No
Esposito, 2011[48]	Yes	Yes	Yes	Yes	Yes
Ferrannini, 2013[194]	Yes	Yes	No	Yes	No
Fonseca, 2012[56]	Yes	Yes	Yes	Not described	Yes
Forst, 2010[57]	Yes	Yes	Yes	Yes	Yes
Gallwitz, 2012[61]	Yes	Yes	Yes	Yes	Yes
Gallwitz, 2012[62]	Yes	Yes	NR/Can't tell	Not described	Yes
Garber, 2011[67]	Yes	Yes	No	Not described	Yes
Genovese, 2013[68]	Yes	Not described	Yes	Yes	Yes
Genovese, 2013[69]	Yes	Yes	Yes	Yes	Yes
Goke, 2010[70]	Yes	Yes	Yes	Yes	Yes
Haak, 2012[77]	Yes	Not described	Yes	Not described	Yes
Haak, 2013[78]	Yes	Yes	Yes	Yes	Yes
Haring, 2014[83]	Yes	Yes	Yes	Yes	Yes
Henry, 2012[84]	Yes	Yes	Yes	Not described	No

Author, year	Randomized	Randomization Scheme	Double-Blind	Blinding Method	Dropouts Description
Henry, 2012[84]	Yes	Yes	Yes	Not described	Yes
Hermans, 2012[87]	Yes	Not described	Yes	Not described	Yes
Hong, 2013[195]	Yes	Yes	Yes	Yes	Yes
Kadowaki, 2013[96]	Yes	Yes	Yes	Yes	Yes
Kaku, 2011[99]	Yes	Not described	No	Not described	
Lavalle-Gonzalez, 2013[106]	Yes	Yes	Yes	Yes	Yes
List, 2009[109]	Yes	Yes	Yes	Yes	Yes
Nauck, 2009[119]	Yes	Yes	Yes	Not described	Yes
Nauck, 2011[120]	Yes	Yes	Yes	Yes	Yes
Nauck, 2014[121]	Yes	Not described	Yes	Not described	Yes
Petrica, 2009[126]	Yes	Not described	No	Not described	Yes
Pfutzner, 2011[128]	Yes	Not described	Yes	Not described	No
Pfutzner, 2011[129]	Yes	Yes	Yes	Not described	Yes
Pratley, 2014[131]	Yes	Not described	Yes	Not described	Yes
Qiu, 2014[132]	Yes	Yes	Yes	Not described	Yes
Reasner, 2011[135]	Yes	Not described	Yes	Not described	Yes
Ridderstrale, 2014[136]	Yes	Yes	Yes	Yes	Yes
Roden, 2013[139]	Yes	Yes	Yes	Yes	Yes
Rosenstock, 2013[144]	Yes	Yes	Yes	Yes	Yes
Ross, 2012[146]	Yes	Yes	Yes	Yes	Yes
Russell-Jones, 2012[147]	Yes	Yes	Yes	Yes	Yes
Schernthaner, 2015[148]	Yes	Yes	Yes	Not described	Yes
Schumm-Draeger, 2015[151]	Yes	Yes	Yes	Yes	Yes
Seino, 2012[156]	Yes	Yes	Yes	Yes	Yes
Stenlof, 2014[213]	Yes	Yes	Yes	Yes	Yes
Suzuki, 2014[161]	Yes	Not described	No	No	No
Umpierrez, 2014[171]	Yes	Yes	Yes	Yes	Yes
Wang, 2015[173]	Yes	Yes	Yes	Yes	Yes
White, 2014[175]	Yes	Yes	Yes	Yes	Yes
Williams-Herman, 2010[177]	Yes	Yes	Yes	Yes	Yes
Xu, 2015[178]	Yes	Yes	No	No	Yes

Author, year	Randomized	Randomization Scheme	Double-Blind	Blinding Method	Dropouts Description
Yang, 2011[180]	Yes	Yes	Yes	Not described	Yes
Yang, 2012[182]	Yes	Yes	Yes	Yes	Yes
Zhang, 2012[187]	Yes	Not described	No	Not described	Yes

Table D10. Characteristics of studies evaluating safety of diabetes medications

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Agarwal, 2005 [189] US RCT	Start year: 2001 End year: 2003 16 Wks	No run-in period	Yes	102/54 Outpatient: subspecialty care setting	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI >40 kg/m^2 <7.5 kg/m^2, class III or IV heart failure, NSAID use
Ahren, 2014[2] Country NR RCT	2009 2013 104 Wks	Yes	Yes	Not Extracted/ 1049 NR	Age <18yr, HbA1c >10.00% or <7.00%, weight <20 or >45 kg/m2, Any liver disease, Any kidney disease, adequate glycemic control while taking background metformin (>=1500mg or maximum tolerated dose) >=3 months before screening, abnormal thyroid-stimulating hormone concentration and not clinically euthyroid, ongoing symptomatic biliary disease, history of pancreatitis, recent clinically significant cardiovascular and/or cerebrovascular disease (<=2 months before screening), treated gastroparesis, history of GI surgery thought to significantly affect upper GI function, history of most cancers not in remission for at least 3 years, personal or family history of medullary thyroid, carcinoma or multiple endocrine neoplasia, type 2, resting systolic blood pressure (SBP)>160mmHg and/or diastolic blood pressure(DBP)>100mmHg,
Alba, 2013[3] Multi-continent RCT Factorial design	Neither year reported 12 Wks	Yes	Yes	Not Extracted/ 211 NR	Age <30 or >65 yr, HbA1c >10% if drug naive, 9% if on antihyperglycaemic agent monotherapy or low-dose combination therapy, 7% if drug naive, 6.5% if on antihyperglycaemic agent monotherapy or low-dose combination therapy, diagnosis >5 years, Any liver disease, Any kidney disease, History of CVD, current use of sitagliptin, vildagliptin, exenatide, PPARr agonist within the prior 12 wks, fasting fingerstick glucose <7.2mmol/l or 14.4mmol/l at week -2
Amador-Licona, 2000 [186] Mexico RCT	12 wks (Planned duration)	Not extracted	No	Not extracted	Age >65 years, any liver disease, history of CVD, other
Andersson, 2010[190] Denmark	1997 2006	Not applicable	Yes	Not Extracted/ 10,920 / 5,852	Age <= 30, No diagnosis/hospitalization for CHF, not using MET, SU and/or Insulin, Use of other glucose lowering meds, patients with previous hospitalisations for HF during the period from 1978 until 1996

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Retrospective cohort	Not applicable			Administrative database	(diagnosis codes [ICD-10] I50, I42, J81, I11.0 and [ICD-8] 425, 4270, 4271) were excluded from the study, not alive 30 days after discharge for CHF, not receiving drug of interest 30 days after discharge for CHF, use of study drug within 90 days of hospitalization fro CHF
Arechavaleta, 2011[5] "multi-national" RCT	Neither year reported 30 Wks	Yes	Yes	Not Extracted/ 1035 NR	Age <18 years, HbA1c >9% or <6.50%, Not on a stable dose of metformin (ГёÑ1500 mg/day) as well as diet and exercise for past 12 wks history of type 1 diabetes, used any Anti Hypoglycemic Agent besides metformin within 12 wks of the screening visit, renal function impairment prohibiting the use of metformin, fasting fingerstick glucose of <6.1 or >13.3 mmol/l at randomization, stable meds for HTN, thyroid dz, HRT, OCPs
Arjona Ferreira, 2013[6] multinational RCT	Neither year reported 58 Wks	Yes	Yes	Not Extracted/ 426 NR	Age <30yr, HbA1c >9.00% or <7.00%, Prior or current use of insulin, Any liver disease, did NOT have moderate to severe chronic renal insufficiency (eGFR>=50 ml/min/1.73m2 using the Modification of Diet in Renal Disease equation), on dialysis or likely to require dialysis for the duratoin of the study, acute renal disease, history of renal transplant, history of ketoacidosis, recent (within 3 months) cardiovascular event, thyroid stimulating hormone outside the reference range, triglycerides>600mg/dl, visit2, FPG>260mg/dl, unlikely to improve with diet/exercise, visite 3, FPG>250mg/dl consistently (i.e., measure=ment repeated and confirmed within 7 days); visite 4, FPG>240mg/dl consistentlyvisit5, finger-stick glucose > 240 or <120mg/dl
Aschner, 2010[7] Multi-continent RCT	Neither year reported 24 Wks	Run-in period but number of participants excluded was NR	Yes	2068/1050 NR	Age <18 and > 78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 6.5% or >9%, treatment naive, no Type 2 DM, FPG <120 mg/dL or >250 mg/dL, triglycerides >600 mg/dL, CK > 2 times normal upper limit
Aschner, 2012[8] Multi-continent	2008 2011 24 Wks	No	Yes	Not Extracted/ 515 NR	Age <35 - >70, HbA1c >=11 or <7, BMI <25 - >45, diagnosis <6 months, Any liver disease, Any kidney disease, FPG >14.4 mmol/L, tx'd w/ oral other than metformin in past 3 mo, received SU+MET In past year, prior use of GLP-1 or DPP-4, any disorder that the investigator felt woudl compromise the patient's safety, unwilling to self-monitor BG or keep

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT					diary
Bailey, 2005 [9] UK, 14 European Countries RCT	24 wks (Planned duration)	Not extracted	Yes	Not extracted	Age <18 or >70 years, history of CVD, no Type 2 DM, other
Bailey, 2013[10] Multi-continent RCT	2007 2008 102 Wks	Yes	Yes	Not Extracted/ 546 NR	Age <18 and >77, HbA1c >10% or 7%, BMI >45 kg/m^2, Any liver disease, Any kidney disease, History of CVD, C-peptide concentration <0.34 nmol/L, not taking stable dose of metformin for at least 8 wks prior to enrollment, creatine kinase more than 3 times upper limit of normal, symptoms of poorly controlled diabetes, systolic blood pressure >=180 mmHG, diastolic blood pressure >=110 mmHG, clinically significant haematological, oncological, endocrine, psychiatric, or rheumatic disease, New York Heart Association class III or IV congestive heart failure
Bakris, 2006 [12] US, Multi-continent, South America, Europe RCT	Neither year reported 32 Wks	Yes	Yes	560/514 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI < 22 kg/m^2, use of any TZD in the 3 months prior to screening, use of insulin for ≥ 6 months at any time prior to screening, anemia, severe angina, SBP >159 mm Hg (can't adjust the BP meds during the trial), DBP >99 mm Hg
Barnett, 2012[13] Multi-continent RCT	2008 2010 52 Wks	Yes	Yes	Not Extracted/ 227 NR	Age <18 or >80 yr, If treatment naive: 10.0%(9.0% for Canada); If receiving an oral antidiabetes drug: 9.0%, If treatment naive: 7.0%; If receiving an oral, antidiabetes drug: 6.5%, BMI >40kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, MI, stokre, or TIA in last 6 months, changed glucose-lowing treatment <10 wks prior to informed consent, hereditary galactose intolerance, treatment with GLP-1 analogue, TZD, or an antiobesity drug within the previous 3 months, or any investigational agent within the previous 2 months, hypersensitivity or allergy to the investigational drugs
Bergenstal, 2010[14]	2008	No	Yes	Not Extracted/	Age <18years, HbA1c >11% or <7.10%, BMI <25 and greater than

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Multi-continent RCT	2008 26 Wks			514 Outpatient: primary care	45kg/m2, Prior or current use of insulin, Prior or current use of study drug, Pregnant, Nursing, Not using adequate contraception, not treated with a stable metformin regimen for at least 2 months before screening, no type 2 diabetes fasting plasma glucose >/= 280 mg/dL (15.5 mmol/L), clinically significant laboratory test values, physical examination, or electrocardiogram results, clinically significant medical condition (e.g., hepatic disease, renal disease, cardiovascular disease, gastroparesis, malignant disease, macular edema, chronic infections), drug or alcohol abuse, donated blood within 60 days of screening or planning to donate blood during study, major surgery or blood transfusion within 2 months of screening, current treatment with alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide, systemic corticosteroids or intrapulmonary steroids, drugs interacting with the CYP2C8 enzyme system, or any investigational drug, known allergies or hypersensitivity to any component of study treatment, or previously experienced a clinically significant adverse event related to TZD or DPP-4 inhibitor use
Bergenstal, 2012[15] Multi-continent RCT	2008 2011 156 Wks	No	Yes	Not Extracted/ 666 clinical sites unspecified	Age <18 years and >75years, HbA1c >10% or <7%, BMI <25kg/m2 and >45kg/m2 (<23 kg/m2 for asians), Prior or current use of insulin, History of CVD, Neuropathy, Retinopathy, were NOT receiving metformin (stable dose >/=1,500 mg/day or maximally tolerated dose for >/=12 wks before screening). diabetic nephropathy, gastrointestinal disease, previous bariatric, surgery, pancreatitis, previous exposure to other oral antihyperglycemic or weightlowering drugs within 12 wks, >1 week of insulin within 6 months, or another GLP-1 mimetic or analog at any time.
Blonde, 2002[16] US RCT	16 wks (Planned duration)	Not extracted	Yes		Age <30 or >75 years, any liver disease, any kidney disease, history of CVD, HbA1c <7.4%, no Type 2 DM, other
Bolinder, 2012[17] Europe RCT	2009 2011 102 Wks	Yes	Yes	Not Extracted/ 182 NR	Women age <55 or >75 years. Men <30 or >75 years, HbA1c >8.50% or <6.50%, BMI <25kg/m^2 and body weight >120 kg, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, Fasting plasma glucose >240 mg/dl (>13.2 mmol/liter), diabetes treatment includes other drugs besides metformin, metformin treatment <1500 mg/d, not on stable metformin treatment at least 12 wks before enrollment, perimenopausal women, body weight change >5% within 3

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					months serum total bilirubin >34 ╣╠ mol/L; hemoglobin (Hb) Γëñ105 g/L (10.5 g/dL) for men and Γëñ95 g/L (9.5 g/dL) for women; abnormal thyroid stimulating hormone level; 25-hydroxyvitamin D level <12 ng/mL (<30 nmol/L), history of osteoporotic fracture, bilateral hip replacement, spinal deformity or spinal surgery, metabolic bone disease or disease known to significantly influence bone metabolism or use of medication known to significantly influence bone metabolism within 6 months of enrolment, T-score less than ΓêÆ2.0 for bone mineral density at lumbar spine, femoral neck, or total hip at baseline DXA measurement, systolic blood pressure ΓëÑ180 mmHg and/or diastolic blood pressure ΓëÑ110 mmHg; cardiovascular event within 6 months of enrolment; congestive heart failure, significant respiratory, hematological, oncological, endocrine, immunological (including hypersensitivity to study medications) alcohol and/or substance misuse disorders; a history of bariatric surgery; use of weight loss medication within 30 days of enrolment
Borges, 2011[18] Multi-continent RCT	2006 2008 80 Wks	No	Yes	Not Extracted/ 688 NR	Age <18 - >75, HbA1c >10.5 or <7.5, BMI < =25, Prior use of any diabetes treatment, fasting glucose <7 mmol/l
Cefalu, 2013[20] Multi-continent RCT	2009 2011 52 Wks	Yes	Yes	Not Extracted/ 1452 NR	Age <18, >80, HbA1c >9.5 or <7, Any kidney disease, Not on stable metformin therapy (ΓëÑ2000 mg per day or ΓëÑ1500 mg per day if unable to tolerate a higher dose) for at least 10 wks, prior TZD use in 16 wks before screening, h/o more than 1 severe hypoglycemic episode within 6 months, repeated measurements of fasting plasma glucose or fasting self-monitored blood glucose, or both, of 15┬╖0 mmol/L or more during the pretreatment phase;
Charbonnel, 2006[21] Multi-continent RCT	Neither year reported 24 Wks	Run-in period but number of participants excluded was NR	Yes	1464/701 NR	Age < 18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >10%, Type 1 DM, insulin use within 8 wks of screening, FPG > 14.4mmol/l
Charpentier, 2001[22]	20 wks (Planned	Not extracted	Yes	Not extracted	Age ≤34 or ≥71 years, any kidney disease, history of CVD, no Type 2 DM, other

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
France RCT	duration)				
Chawla, 2013[23] India RCT	2008 2009 16 Wks	No	No	Not Extracted/ 52 NR	Age <18yr, HbA1c >11% or <7.50%, Any liver disease, Any kidney disease, History of CVD, not on met monotherapy of >=1500mg/day for at least 1 month, FPG<140mg/dl or >270 mg/dl
Chien, 2007[24] Taiwan, Multi-center RCT	Neither year reported 16 Wks	No run-in period	Yes	166/100 5 medical centers. Does not specify inpatient or outpatient	Age <30 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, retinopathy, HbA1c >12% and FPG>250 mg/dL at screening visit, HbA1c <7% and FPG<140 mg/dL at screening visit, BMI <18.5 or >35 kg/m^2, current significant GI disorder, hyperosmolar nonketotic coma, hypersensitivity to glyburide or metformin, current infection, treatment with insulin in last 6 months, surgery in past 4 wks, history of cancer in 5 years, on concurrent drugs affect sugar metabolism, FPG < 140 mg/dl at second visit, not on a stable dose of SU at baseline or dose of metformin>1000mg/day or SU dose too low (glyburide or glicazide<10 mg/day, glimepiride<4mg/d, glicazide<160mg/d)
Comaschi, 2007[25] Italy RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	Yes	398/250 NR	Age <35 years, HbA1c <7.5% or >11%, had not received SU or metformin as a monotherapy at a stable dose for at least 3 months, fasting C-peptide <0.33nmol/L
Curkendall, 2014[216] US	2009 2010 Not applicable	Not applicable	Yes	Not Extracted/ 22,592 Administrative database	Age <18, less than 180 days continuous insurance eligibility prior to index date, used insulin or other dm2 drug (other than met, su or saxa) within 180 days prior to index date, did not have a metformin prescription within 180 days prior to the index date, did not receive metformin on or after the index date, did not have 120 days of continuous insurance coverage immediately after the index date, did not have a subsequent saxa or SU prescription after the index date, gestational diabetes or dm1 during study perioddid not have a code for dm2 during study period

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Retrospective cohort					
Currie, 2009 [217] Taiwan Prospective or retrospective cohort	Start year: 2000 End year: 2005 6 Years	NA	NR	1432850/473483 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Type 1 DM, prescribed insulin only during study period, new diagnosis of Type 2 DM during the year before index date, switch between rosiglitazone and pioglitazone or combined use of both drugs during study period, prescribed ODM less than three times during study period
Davies, 2007[26] United Kingdom RCT	Neither year reported 4 Months	Run-in period but number of participants excluded was NR	NR	82/NR NR	Age <30 or >80 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c <7.0%, BMI >43 kg/m^2, not using adequate contraception, history of previous insulin use for >2wks, duration of Type 2 DM <12 months, C-peptide levels <0.33, severe concurrent disease, serum creatine >150umol/l
Davies, 2013[218] Country NR RCT	Neither year reported 26 Wks	Yes	Yes	Not Extracted/ 222 NR	Age <18yr, HbA1c >10.00% or <7.10%, BMI <25 or >45kg/m2, or unstable, weight(>5% variability) for 3 months, Not using adequate contraception, not on following therapy: stable dose of met(>1000mg/day) alone or in combination with with a stable dose of SU as a separate formulation for at least 3 months before randomization, have a clinically significant medical condition that could preclude safe participation in this study, had more than 3 major hypoglycemic episodes in the past 6 months, had been treated with a drug that promotes weight loss within 3 months of screening
DeFronzo, 1995[27] +US RCT	29 wks (Planned duration)	Not extracted	No	Not extracted	Age <40 or >70 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
DeFronzo, 2005[28] US	2002 2003	Yes	Yes	NR/336 NR	Fasting glucose >13.3 mmol/l. Not on metformin >=1500mg/day for at least 3 months before screening. If weight not stable (=/-10%) for 3 months before screening. Female subjects were not postmenopausal,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT	30 wks				surgically sterile, or using contraceptives for 3 months before screening and continuing throughout the study. Use of sulfonylureas, meglitinides, thiazolidinediones,-glucosidase inhibitors, exogenous insulin therapy, weight loss drugs, corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug, or e.
DeFronzo, 2009[29] NR RCT	Neither year reported 24 Wks	Yes	Yes	1462/743 NR	Age >18 and <77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), contraindication or history of intolerance to metformin, neuropathy, retinopathy, HbA1c < 7% or >10%, BM >40 kg/m^2, pregnant, nursing, alcohol or drug abuse, NYHA III and IV, LVEF <40
Defronzo, 2010[30] United States RCT	Start year: 2006 End year: 2008 20 Wks	None	Yes	NR/137 NR	Age <18 or >75 years, HbA1c <6.8% or >10%, BMI <25 kg/m^2 or >40 kg/m^2, not on stable dose of metformin for at least 6 wks, body weight stable for past 6 months, islet cell auto-antibodies, treatment with any other antidiabetic medication (other than metformin)
DeFronzo, 2012[31] Multi-continent RCT	Neither year reported 26 Wks	Yes	Yes	Not Extracted/ 1554 NR	Age <18 or >80 yr, HbA1c >10% before and after run-in/stabilization period, 7.5% before and after run-in/stabilization period BMI <23 or >45kg/m2, Any liver disease, Any kidney disease, Retinopath, Not using adequate contraception, fasting C-peptide <0.26nmol/l, not on met monotherapy (stable met dose >1500mg/d for >=2 months), SBP/DBP>160/100mmHg, hemoglobin < 12g/dl for men, <10g/dl for women, class 3 or 4 CHF, cardiac surgery or acute MI within last 6 months, TSH > ULN, treated diabetic gastroparesis, no willingness or ability to perform self-monitoring of blood glucose or to provide written informed consent, FPG>16.7mmol/l after run-in/stabilization period, oral or systemically injected glucocorticoids or weight-loss drugs within 3 months of randomization
Del Prato, 2015[32] Multi-continent	Neither year reported 208 wks	No	Yes	NR/814 NR	NR

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT					
Del Prato, 2014[33] Multi-continent RCT	Neither year reported 104 wks	Yes	Yes	NR/2639 NR	Systolic blood pressure >150mm hg. Diastolic blood pressure >90 mm hg. History of cancer. Prior use of any other diabetes drug for the last 2 months.
Derosa, 2004 [34] Italy RCT	12 months (Planned duration)	Not extracted	No	Not extracted	Age <46 or >67 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other
Derosa, 2009[38] Italy RCT	Neither year reported 15 Months	Fewer than 10% of participants were excluded during run-in	NR	271/252 Outpatient: primary care, computerized clinic registry	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c < 6.5%, BMI <25 kg/m2 or >30 kg/m2, pregnant, nursing, not using adequate contraception, no Type 2 DM, history of ketoacidosis, severe anemia
Derosa, 2010 [39] Italy RCT	Neither year reported 12 Months	No run-in period	No	128/128	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c < 8%, BMI <25 kg/m^2 or ≥30 kg/m^2, pregnant, nursing, not using adequate contraception, history of ketoacidosis, severe anemia, not intolerant to metformin at maximum dosage (3,000 mg/day), not on metformin, diabetic neuropathy
Derosa, 2005[36] Italy RCT	Neither year reported 12 Months	No run-in period	NR	NR/99 case notes and/or clinic registers	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment),

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					neuropathy, retinopathy, HbA1c < 7%, pregnant, nursing, not using adequate contraception, no type 2 DM by ADA criteria for at least 6 mo, fasting c-peptide <1.0ng/ml, no metabolic syndrome with at least 3 components (based on NCEP ATP III), ketoacidosis, anemia, cerebrovascular conditions within 6 months, consumption of glimepiride or TZDs or prior intolerance to these medications
Derosa, 2005[37] Italy RCT	12 months (Planned duration)	Not extracted	No	Not extracted	Age <18 years, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <7.5%, no Type 2 DM, other
Derosa, 2013[42] Italy RCT	2008 2010 12 Months	Yes	Not reported	Not Extracted/ 178 NR	Age <=18yr, HbA1c <=7.5%, BMI <25 or >=31 kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, ketoacidosis, severe anemia, New York Heart Association 1-4 congestive heart failure
Derosa, 2013[43] Italy RCT	2008 2010 12 Months	Yes	No	Not Extracted/ 171 NR	Age <=18yr, HbA1c <=7.5%, BMI<25 or >=34.9kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, history of ketoacidosis, acute or chronic pancreatitis, severe anemia, serous CVD (e.g. New York Heart Association class 1-4 CHF, MI, stroke) or cerebrovascular conditions within 6 months before study enrollment, taking gygtemic glucocorticoids, taking weight reducing drugs such as sibutramine or orlistat, or any medications that miht preclude safe participation in the study
Diamant, 2010[44] Multi-continent RCT	2008 2009 26 Wks	Yes	Yes	Not Extracted/ 321 NR	Age 18 years or older, HbA1c >11 or <7.1, BMI <25kg/m2 and >45kg/m2. Unstable body weight within 3 months, more than three episodes of major hypoglycaemia within 6 months of screening, treatment within 4 wks of screening with systemic glucocorticoidstreatment for longer than 2 wks with insulin, thiazolidinediones, ╬▒-glucosidase inhibitors, meglitinides, exenatide twice-aday formulation, dipeptidyl peptidase-4 inhibitors, or pramlintide acetate within 3 months of screening, not treated with a stable dose of metformin of 1500 mg or more per day for at least 8 wks prior to screening
Dormuth,	Start year:	NA	No	127581/	Had received insulin or other ODMs besides metformin, SU or TZD,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
2009[219] Canada Prospective or retrospective cohort	1998 End year: 2007 11 Years			84339 Community	gestational DM, fractures, admitted to long term facility
Einhorn, 2000[45] US RCT	16 wks (Planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <8.0%, no Type 2 DM, other
Erem, 2014[47] Turkey RCT	Neither year reported 52 Wks	Yes	No	Not Extracted/ 60 NR	Age <30 or >70 yr, HbA1c >8% when FPG<126mg/dl, <7% if FBG is 126 -139 mg/dl and HOMA-IR>3, not newly diagnosed, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, COPD, ketoacidosis or ketonuria, NYHAC Class 3/4 CHF history of lactic acidosis, malignancy, thyroid disease or chronic inflammatory diseases or rheumatic disease, substance abuse, steroid treatment, active infection
Esposito, 2011[48] Italy RCT	Neither year reported 24 Wks	No	Yes	Not Extracted/ 110 investigators' practices	Age <30 and >75 years, HbA1c >10% or <7%, BMI </=25kg/m2 and unstable weight in last 6 months or evidence of participation in weight reduction programs, "Newly diagnosed", Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Pregnant, Nursing, any investigational drug in past 3 mo, use of agents affecting glycaemic control (such as systemic glucocorticoids and weight loss drugs), acute disease or infection, recent (within 3 months) cardiovascular events or surger, immunological disorders, any condition that might compromise adherence to the study, patients with positive antibodies to glutamate decarboxylase, participation in weight loss program or unstable wt in past 6 mo, patients with C-peptide levels less than 0.25 pmol/l (<0.76 ng/l)
Farcasiu, 2011[51] Multi-continent	2006 2009 16 Wks	Yes	Yes	Not Extracted/ 302 NR	Age <30 - >75, 1.8 X ULN, 1.2 X ULN, BMI >40, Any liver disease, metformin <1500mg, on other oral dm med besides metformin, history of severe hypoglycemia within 6 months, CHF, renal transplantation, irregular sleep-wake cycle

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT					
Feinglos, 2005[52] US RCT	16 wks (Planned duration)	Not extracted	Yes	Not extracted	Age <30 or >81 years, any liver disease, any kidney disease, history of CVD, HbA1c <7.0% or >8.5%, no Type 2 DM, other
Ferrannini, 2013[53] Multi-continent RCT	Neither year reported 90 Wks	Yes	Yes	Not Extracted/ 659 NR	Age <18 or>79, HbA1c >=10 or 7, BMI>40, successfully completed one of the two 12-wk dose-finding studies (refid 584 or 1334)
Ferrannini, 2013[194] Multi-continent RCT	Neither year reported 12 Wks	Yes	Yes	Not Extracted/ 408 NR	Age <18 or >79, HbA1c >9 if on antidiabetic drug, >10 if tx naïve, 6.5 if on antidiabetic drug, <7 if treatment naïve, BMI >40, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, not treatment naive or on stable dose of more than one antidiabetic drug (except GLP1, insulin, TZDs) in past 10 wks, myocardial infarction, stroke or transient ischaemic attack Γëñ6 months prior, unstable or acute congestive heart failure, acute or chronic acidosis; disease of CNS, psychiatric d/o or clinically relevant neuro d/o, chronic or clinically relevant acute infection, current or chornic urogenital tract inf, dehydration, hereditary galactose intolerance, tx with antiobesity drugs, systemic steroids, alchol abuse, tx with investigational drug <=2 m prior neurologic/psychiatric issues that might interfere with participation
Fonseca, 2000 [55] US RCT	26 wks (Planned duration)	Not extracted	No	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no type 2 DM, other
Fonseca, 2012[56] US and Latin America RCT	2009 2010 18 Wks	Yes	Yes	Not Extracted/ 282 NR	Adults, HbA1c >11 or <7.5, BMI >45, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Not using adequate contraception, weight loss >10% in 3 mo before screening, unable to finish lead-in period (stabilitized on met 1500 mg/d), history of ketoacidosis, alcohol or drug abuse or unstable psychiatric disorder, hemoglobinopathy, blood/plasma donation in past 3 mo, anemia or

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					significant lab/ecg abnormalities, investigational drugs or partiipation in a clinical trial in last mo, treatment with any other diabetes med (besides met) in past 8 wk, tx with potent CYP 450 3A drug or contradind to / h/o tx w/ saxa
Forst, 2010[57] Europe RCT	Neither year reported 12 Wks	Yes	Yes	Not Extracted/ 333 NR	Age <21 or >75 yr, HbA1c >9.0% for patients previously treated with met and one other oral anti-diabetic drug; 10.0% for patients perviously treated with met alone; 10% for all patients after run-in phase, 7.0% for patients previously treated with met and one other oral anti-diabetic drug; 7.5% for patients previously treated with met alone; 7.5% for all patients after run-in phase, BMI <25 or >40 kg/m2, diagnosis <3 months, Prior or current use of insulin, previously treated with therapy other than 1. met alone; 2. met and one other oral hypoglycaemic agent other than rosi or pio., anti-diabetic therapy changed within 10 wks prior to screening, FPG concentrations > 13.3mmol/l (measured on 2 separate days), treated with rosi or pio within 6 months prior to screening one or more of a list of specified clinical lab abnormalities (not specified in article), clinically relevant stroke, MI, TIA within 6 months
Forst, 2014[59] Germany RCT	Neither year reported 12 Wks	No	Yes	Not Extracted/ 40 Outpatient but unclear if primary or specialty care	Age <45 or >75yr, HbA1c >8.5 or <6.5, Any liver disease, Any kidney disease, more than one unexplained episode of severe hypoglycaemia within 6 months, pre-treatment with anti-diabetic drugs other than metformin within the last 3 months, uncontrolled hypertension (SBP>160mmHg, and/or DBP>90mmHg), MI or stroke in last 6 month
Gallwitz, 2011[60] Germany RCT	Neither year reported 26 Wks	No	Yes	Not Extracted/ 363 NR	Adults, HbA1c >10 or <6.5, not on metformin
Gallwitz, 2012[61] Multi-continent RCT	2008 2010 104 Wks	Yes	Yes	Not Extracted/ 1552 Outpatient: primary care Outpatient:	Age <18, >80 years, BMI >40 kg/m^2, Prior or current use of insulin, Any liver disease, History of CVD, Not on stable metformin dose >= 1500mg/day (alone or with another antidiabetic drug), HbA1c <6.5% or >10% if participant on metformin alone prior to enrollment, HbA1c <6% or >9% if participant on metformin and another anti-diabetic medication prior to enrollment, myocardial infarction, stroke, transient ischemic

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
				subspecialty care setting	attack 6 months prior to screening, treatment with rosiglitazone, pioglitazone, GLP-1 analogue or agonist 3 months prior to screening, On anti-obesity drug in 3 months prior to screening
Gallwitz, 2012[62] Multi-continent RCT	2006 2011 48 Months	No	Yes	Not Extracted/ 1029 NR	Age <18 or >85, HbA1c >9 or <6.5, BMI <25 or >=40, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, adequate response to metformin based on HbA1c criteria, contraindication to glimepiride, active/untreated cancer or cancer in remission <5 yrs, hemoglobinopathy or significant anemia, severe GI disease, on drugs affecting motility, glucocorticoids, weight loss drugs in last 3 mo, treatment for more than 2 wks in past 3 mo with insulin, TZDs, alpha glucosidase inhib, SUs, meglitinides
Garber, 2009[66] United States, Mexico RCT	Start year: 2006 End year: 2007 52 Wks	Fewer than 10% of participants were excluded during run-in	Yes	NR/746 NR	Age <18 or >80 years, HbA1c <7% or >11% if prior treatment was diet; >10% if prior treatment was drug, BMI >45 kg/m^2, either not treated with diet and exercise or up to half the highest dose of ODM monotherapy for at least 2 months prior to trial, insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia, impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations 5 times upper normal range)
Garber, 2002[63] US RCT	20 wks (Planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, treatment experienced, HbA1c <7% or >11%, no Type 2 DM, other
Garber, 2003 [64] US RCT	16 wks (Planned duration)	Not extracted	Yes	Not extracted	NR
Garber, 2006[65]	24 wks	Not	Yes	Not extracted	Age <20 or >78 years, any liver disease, any kidney disease, history of

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
US RCT	(Planned duration)	extracted			CVD, HbA1c ≤7.0% or ≥12.0%, no Type 2 DM, other
Garber, 2011[67] US Mexico RCT	2006 2008 104 Wks	No	Yes	Not Extracted/ 746 NR	Age <18 or >80, HbA1c >11% if on diet/exercise or >10% if on monotherapy, 7%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia
Genovese, 2013[68] Italy RCT	Neither year reported 24 Wks	Yes	Yes	Not Extracted/ 213 NR	Age <35 or >75 yr, Any liver disease, Any kidney disease, Pregnant, Nursing, Not using adequate contraception, not taking metformin (2000-30000mg/day) for at least 3 months, HDL-C levels >=40mg/dl in males and >=50mg/dl in females irrespective of statin tx, anemia of any etiology (Hb<10.5g/dl) or any other hematological disease; diagnosis or suspicion of neoplastic disease, no central obesity (excluded if waist circumference <94 cm for men and <80 cm for women), using oral anti-diabetic drugs other than met or insulin in the 3 months preceding study entry, treatment with fibrates or rifampicin acute or chronic pancreatitis or familial polyposis history of chronic alcohol or, drug/substance abuse, satisfactory drug compliance (compliance ranging between 80-120%) during run-in, medical history of MI, transient ischemic attacks or stroke in the past 6 months, designation of class 1-4 heart failure according to NYHA criteria
Genovese, 2013[69] Country NR RCT	Neither year reported 16 Wks	Yes	Yes	Not Extracted/ 58 Outpatient: subspecialty care setting	Age <35 or >75 yr, HbA1c >9.00%, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, lack of cooperative attitude and ability to be treained to use the investigational drugs correctly or to attain the study procedures participation in another trial in the 3 months preceding study entry, any disease with malabsorption, or familial polyposis or pancreatitis, congestive heart failure (NYHA class 1-4), anemia of any etiology (hemoglobin level < 10.5g/dl) or any other clinically relevant hematologic disease, diagnosis or suspicion of any neoplastic disease, history of chronic alcohol or drug/substance abuse, or presence of other conditions potentially able to affect study stubjects compliance, concomitant therapy

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					with statins, antioxidant drugs (e.g. vitamins, Q10 coenzyme), beta-blockers, nonsteroidal anti-inflammatory drugs, aspirin, corticosteroids,known allergy, sensitivity, ,or intolerance to study drugs and/or study drugs' formulation ingredients (pioglitazone, met marked above)
Goke, 2010[70] Multi-continent RCT	2007 2010 104 Wks	Yes	Yes	Not Extracted/ 858 NR	Age <18 years, HbA1c >10% and <6.50%, Prior or current use of insulin, Prior or current use of study drug, Any liver disease, Any kidney disease, no type 2 diabetes, not on stable metformin monotherapy >=1500mg/day for at least 8 wks prior to enrollment, type 1 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, donation of blood, plasma or platelets within the 3 months prior to enrolment, history of haemoglobinopathies; significant alcohol or drug abuse within the year prior to enrolment, treatment with human immunodeficiency virus Γüä antiviral drugs or cytochrome P450 3A4 (CYP450 3A4) inducers, treatment with a thiazolidinedione within 12 wks prior to enrollment congestive heart failure, significant cardiovascular history within the past 6 months
Goldstein, 2003[71] US RCT	18 wks (Planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, HbA1c <7.5 and >12.0, other
Goldstein, 2007[72] Multi-continent RCT	Neither year reported 24 Wks	Run-in period but number of participants excluded was NR	Yes	3544/1091 NR	Age <18 or >78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), patient with < 75% compliance during placebo run in period, patient with HbA1c <7.5% or >11 % after diet/exercise run in/wash-out period, patients with fasting glucose > 280 mg/dl after run-in period, no Type 1 DM or Type 2 DM
Gomez-Perez, 2002[73] Mexico RCT	26 wks (Planned duration)	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Gupta, 2013[76] India RCT	2012 2013 24 Wks	No	NR	Not Extracted/ 167 Outpatient: primary care	Any liver disease, Any kidney disease, Pregnant, Nursing, hx of hypersensitivity to sulphonylurea and DPP-IV inhibitors psychiatric, GI, hematological, metabolic, neurological, hepatic, or renal disorders, clinically significant heart disease (NYHA III or IV), acute infection
Haak, 2012[77] Multi-continent RCT	2008 2010 24 Wks	Yes	Yes	Not Extracted/ 791 NR	Age <18 or >80 years, HbA1c >10.5% if on OAD or >=11% if treatment naïve 7.0% if on OAD or <7.5% if treatment naïve, BMI > 40 kg/m2, Prior or current use of insulin, Any kidney disease, History of CVD, Pregnant, Nursing, neither treatment naive nor had been treated with OAD monotherapy, prior treatment with rosiglitazone, pioglitazone, GLP-1 analogs, or anti-obesity drugs in the previous 3 months, receiving treatment with systemic steroids or had a change in dosage of thyroid hormones in the previous 6 wks, had undergone gastric bypass, Had known hypersensitivity or allergy to linagliptin or its excipients, metformin or placebo, had a history of alcohol or drug abuse in the previous 3 months, had acute or chronic metabolic acidosis, had hereditary galactose intolerance, had experienced a myocardial infarction, stroke, or transient ischemic attack in the previous 6 months
Haak, 2013[78] Multi-continent RCT	2009 2011 52 Wks	Yes	Yes	Not Extracted/ 567 NR	Pregnant, Nursing, Not using adequate contraception, completed the previous 6-month trial, were not on rescue medication alcohol abuse within the past 3 months or drug abuse that would have interfered with trial participation
Hamann, 2008[80] Multinational Europe, Mexico RCT	Neither year reported 52 Wks	Yes	NR	818/596 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >10%, BMI <25 kg/m^2, used any ODM other than metformin in the prior 12 wks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin < 11.0 g/ dl for men and < 10.0 g/

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					dl for women), C-peptide <0.5nmol/L, SBP >170mmHg, DBP >100mmHg
Hanefeld, 2004[81] Canada, UK, Hungary, Finland, U.K., Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and the Netherlands RCT	NR	Not extracted	Yes	Not extracted	Age <35 or >75 years, history of CVD, HbA1c <7.5% or >11%, no Type 2 DM, other
Hanefeld, 2007[82] Multinational Europe RCT	Neither year reported 52 Wks	Run-in period but number of participants excluded was NR	Yes	NR/598 NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI <22 kg/m^2 or >38 kg/m^2, pregnant, patient on insulin therapy, patient with diabetic complications requiring treatment, hematologic impairment, FPG <7mmol/l or > 15mmol/l, C-peptide <0.27 nmol/l
Haring, 2014[83] Multi-continent RCT	2010 2012 24 Wks	Yes	Yes	Not Extracted/ 638 NR	Age <18, HbA1c >10 or <7, BMI >45, Any liver disease, Contraindication or history of intolerance to metformin, not on stable MFM IR unchanged >=12 wks prior to randomization, uncontrolled hyperglycemia (glu> 13.3mmol/L) after overnight fast confirmed by 2nd measurement, ACS, stroke, TIA within 3 mo, bariatric surgery or other GI surgeries that induce chronic malabsorption, cancer (except basal cell ca) or tx for CA within last 5 yrs, blood dyscrasias, hemolysis, unstable erythrocytes, tx with antiobesity drugs 3m prior, use of tx leading to unstable body weight, tx with systemic steroids, change in dose of thyroid hormones within 6w, alcohol or drug abuse within 3m, investigational drug in another trial with 30d eGFR<30
Henry, 2012[84]	2008 2009	Yes	Yes	Not Extracted/ 603	Age <18 or >77, HbA1c >12 or <7.5, BMI >45, Any liver disease, Any kidney disease, creatine kinase > 3 times ULN;, h/o diabetes insipidus,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Multi-continent RCT	24 Wks			Inpatient/hospital Outpatient: primary care Outpatient: subspecialty care setting	symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), New York Heart Association Class III or IV congestive heart failure, systolic blood pressure ΓÇí 180 or diastolic blood pressure ΓÇí 110 mmHg., a cardiovascular event within 6 months, other significant renal, hepatic, hematologic, oncologic, endocrine, psychiatric, or rheumatic disease
Henry, 2012[84] Multi-continent RCT	2009 2010 24 Wks	Yes	Yes	Not Extracted/ 641 Inpatient/hospital Outpatient: primary care Outpatient: subspecialty care setting	Age <18 or >77, HbA1c >12 or <7.5, BMI >45, Any liver disease, Any kidney disease, History of CVD, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), New York Heart Association Class III or IV congestive heart failure, systolic blood pressure ΓÇí 180 or diastolic blood pressure ΓÇí 110 mmHg., a cardiovascular event within 6 months
Hermann, 1994[86] Sweden RCT	6 months (Planned duration),	Not extracted	Yes	Not extracted	No Type 2 DM, other
Hermans, 2012[87] Europe RCT	Neither year reported 24 Wks	Yes	Yes	Not Extracted/ 286 NR	Age <18, HbA1c >10 or <7, Prior or current use of insulin, Contraindication or history of intolerance to metformin, Pregnant, Nursing, type 1 DM, history of DKA or HONC, prior use of injectable GLP-1 analogues within 3mo of study, treatment with systemic glu-cocorticoids other than replacement therapy (inhaled, local injected and topical use of glucocorticoids were allowed), treatment with cytochrome P450 3A4 inducers, not on stable tx with metfomrin 1500-1700 mg/d
Hong, 2013[195] China	2004 2007 36	Yes	Yes	Not Extracted/ 304 clinical centers	Age >80yr, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, not diagnosed as CAD (either having a history of acute myocardial infarction diagnosed by a representative set of,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT	Months				electrocardiograms, cardiac enzyme values, and typical symptoms or by angiographically identified stenosis of >50% of lumen diameter in at le, severe dysfunction of the heart (NYHA class > phase 3), other severe organic heart diseases, including but not limited to congenital heart disease, rheumatic heart disease, hypertrophic or dilated, cardiomyopathy;, psychiatric disease, severe infection, severe anemia, neutropenia, allergic to study drugs, fasting plasma glucose>=15 mmol/l, recent drug or alcohol abuse
Jadzinsky, 2009[91] Multi-continent RCT	Start year: 2006 End year: 2007 24 Wks	Fewer than 10% of participants were excluded during run-in	Yes	2936/1394 Outpatient: primary care, Outpatient: subspecialty care setting, Community	Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), HbA1c< 8% >12%, BMI >40 kg/m^2, prior treatment, diabetic ketoacidosis or nonketotic hyperosmolar coma, CVD events 6 months prior, LVEF <40%, psychiatric history, alcohol or drug abuse, abnormal metabolic or hematologic test
Jain, 2006 [92] US, Puerto Rico RCT	Neither year reported 56 Wks	Run-in period but number of participants excluded was NR	NR	NR/502 NR	Age <18 or >80 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. failed initial treatment), HbA1c < 7.5% or >11.5%, pregnant, nursing, duration of DM > than 2 years, intolerance to rosiglitazone, pioglitazone or troglitazone, drug or alcohol abuse, previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin , SU for 3 months or more, use of hydrochlorothiazide, joint injections, niacin > 250 mg/day, ODM, concurrent participation in another investigational study, serum creatinine level > 1.5mg/dl of men, 1.4 mg/dl for women, 1 + proteinuria, anemia(< 10g/dl women, < 12g/dl men, BMI <20 kg/m^2 or >45 kg/m^2; hypertension, chronic pulmonary disease, history of cancer not in remission for at least 5 years
Ji, 2015[93] Multi-continent	2011 2013	Yes	Yes	NR/689 NR	Age <18 or >80, HbA1c>10, HbA1c7, BMI or weight >45, prior use of any diabetes treatment, prior or current use of insulin, prior or current use of study drug, any liver disease, any kidney disease, contraindication or

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
RCT	14 wks				history of intolerance to metformin, pregnant, nursing, bariatric surgery, cancer, blood dyscrasia, pancreatitis, treatment with anti-obesity drugs within 3 months before consent or any other treatment at the time of screening leading to unstable body weight, glucose >240 mg/dl, acute coronary syndrome, stroke, or transient ischemic attack within 3 months before consent, treatment with systemic steroids, change in dosage of throid hormones within 6 weeks
Jones, 2003[202] US RCT	Neither year reported 6 Months	Run-in period but number of participants excluded was NR	NR	NR/N: NR	Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, CHF, history of chronic insulin, FPG <140 or >300 mg/dL, prior rosiglitazone study, use on any investigational drug within 30 days
Kadoglou, 2011[95] Greece RCT	2006 2008 6 Months	No	No	Not Extracted/ 140 NR	Age <50 and >75, HbA1c <=7%, BMI <=25kg/m2, Any liver disease, Any kidney disease, usage of antidiabetic medications, autoimmune or life threatening illnesses, on diet therapy for diabets for at least 3 mo, congestive heart failure (NYHA class IIIV), clinical evidence of cardiovascular (coronary, peripheral arteries), autoimmune or life-threatening diseases, alcohol / drug abuse, uncontrolled hypertension (blood pressure > 170 / 100 mmHg), recently diagnosed / or untreated hormonic disorders, free from microvascular compl, maintained body weight for 3 mo before study
Kadowaki, 2013[96] Japan RCT	2006 2008 12 Wks	Yes	Yes	Not Extracted/ 149 NR	Age <20 or >=75yr, 9.4% for patients receiving an OHA other than met at screening, 10.5% for patients with met only at screening, 10.5% for all patients completing the run-in period, 6.4% for patients receiving an OHA other than met at screening, 6.9% for patients with met only at screening, 6.9% for all patients completing the run-in period, Any kidney disease, high serum creatinine levels (male > 100.8umol/l, female>78.7umol/l), FPG>15.0mmol/l at the beginning of the placebo run-in period, not on stable diet and exercise therapy for at least 8 wks, not on met monotherapy for at least 12 wks
Kahn, 2006 [97]	Start year: 2000 End year:	No run-in period	Yes	6676/4360 NR	Age < 30 or > 75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Multi-continent RCT	2006 6 Years				or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), uncontrolled hypertension, fasting plasma glucose <126 or > 180 mg/dL, history of lactic acidosis
Kahn, 2008 [220] US, Multinational Europe RCT	Neither year reported 4 Years	No run-in period	Yes	4360/4351 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), history of lactic acidosis, uncontrolled hypertension, corticosteroid use
Kaku, 2009 [98] Japan RCT	Start year: 2005 40 Wks	Yes	Yes	NR/236 NR	Age ≤20 or ≥65 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. failed initial treatment), HbA1c <6.5% or >10%, other pre-existing conditions that potentially require hospitalization such as cancer, severe lung, gastrointestinal, pancreatic and hematological disorders, history of lactic acidosis, ketoacidosis, diabetic coma, or pre coma within the preceding 26 wks, if on any medications that might affect glycemic control, drug or alcohol dependency
Kaku, 2011[99] Japan RCT	2006 52 Wks	Yes	Yes	Not Extracted/ 411 NR	Age <20, HbA1c >10.4 or <7.4, not able to self monitor blood glucoses
Karter, 2005 [221] US Cohort	Start year: 1999 End year: 2001 10 Months	NA	No	NA (for cohort studies, claims data, etc)/23440 managed care organization	CHF, no pharmacy benefit, Type 1 DM, >80% pill adherence, filled a refill of index medication, member of health plan >1 year, any utilization of the index therapy in the 12 months prior to initiation of the study
Kikuchi, 2012[101] Japan	2005 2007	No	Yes	Not Extracted/ 373	Age <20 - >75, HbA1c <7.4, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Retinopathy, hyperlipidemia w/o statin tx, SBP >=160 or DBP >=100, FPG >=270, BNP >= 60,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
	28 Wks			NR	hemoglobinopathy Edema, unstable or serious angina, MI in past yr, h/o or current heart failure, serious arrhythmia, valvular dis, cardiomyopathy serious neuropathy requiring tx
RCT fixed titration of both drugs during tx period					
Kim, 2014[103] South Korea RCT	2007 2009 26 Wks	Yes	Yes	Not Extracted/ 209 NR	HbA1c >10 or <7, 3 months, Pregnant, treated with metformin 500-1000mg alone for at least 4 wks prior to study unable to complete diary to monitor SMBG acute complications such as diabetic ketoacidosis, hyperglycemic hypoerosmolar state within 3 months clinically significatn renal or hepatic disorders
Komajda, 2010 [222] Multi-continent RCT	Start year: 2001 End year: 2003 5.5 Years	None	Yes	NR/4447	Age <40 or > 75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c ≤7% or > 9%, BMI ≤25 kg/m^2, planned cardiovascular intervention, uncontrolled hypertension, no Type 2 DM, current use of other anti-DM medications, hospitalization within last 3 months for CVD event, heart failure
Kvapil, 2006[105] Multinational Europe RCT	Neither year reported 16 Wks	No run-in period	NR	NR/341 NR	Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, recurrent severe hypoglycemia, anemia, change in dose of meds known to interfere with glucose metabolism, adequately controlled on metformin
Lavalle-Gonzalez, 2013[106] Multi-continent RCT	Neither year reported 56 Wks	Yes	Yes	Not Extracted/ 1284 NR	Age <18 or >80, HbA1c >10.5 or <7, Prior or current use of insulin, Any kidney disease, not on MFM (ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose], repeated FPG and/or fasting self-monitored blood glucose (SMBG) ГëÑ15.0 mmol/l during the pretreatment phase, Type 1 diabetes, treatment with a peroxisome

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					proliferator-activated receptor ╬┤ agonist, insulin, another SGLT2 inhibitor or any other AHA (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 wks before screening;, cardiovascular disease (including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening, uncontrolled HTN
Lee, 2013[223] S. Korea Prospetive cohort	2011 2013 24 Wks	Not applicable	No	Not Extracted/ 116 Outpatient: subspecialty care setting	HbA1c >7.5, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, hematologic disease, GI disease systemic steroids in past 12 wks, recent (Γëñ6 months) history of major cardiovascular event, including myocardial infarction, unstable angina, moderate to severe congestive heart failure, and/or stroke. first time visitors to diabetes center
Lehman, 2012[224] US Retrospective cohort	1999 2006 Not applicable	Not applicable	No	Not Extracted/ 5042 Veteran's Large Health Survey + VA databases with medicaiton and encounter information	Age <19 or >90, Female, Any liver disease, Any kidney disease, did not have prescription of SU or MFM solely for 180 days or more, PCa event occuring within 180 days of MFM or SU baseline exposure, prescription for Ins or TZD during study period, CA dx before baseline, missing data on baseline covariates (age, ethnicity, HbA1c, BMI, diabetes dur, Charlson comorbidity score, smoking status), did not have at least 1 primary care and 1 dm2 encounter per year 1999 to 2000
Leiter, 2005 [108] Canada RCT	Neither year reported 32 Wks	No run-in period	Yes	720/613 Outpatient: primary care	Age <20 or >80 years, HbA1c < 9.5%, no Type 2 DM, FBG <7 but >14mmol/L
List, 2009[109] US Canada	2005 2006 12 Wks	Yes	Yes	Not Extracted/ 389 "98 clinical centers"	Age <18, >79, HbA1c >10 or <7, BMI >40, Prior use of any diabetes treatment, Any kidney disease, C peptide>1.0 ng/ml

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Mexico, Puerto Rico RCT					
Madsbad, 2004[110] Multinational Europe RCT	Start year: 2000 End year: 2001 12 Wks	No run-in period	Yes	311/193 Outpatient: primary care, Outpatient: subspecialty care setting, Community	Age <30 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), HbA1c < 7.5% or >10% on diet treatment, BMI >40 kg/m^2, pregnant, nursing, not using adequate contraception, no Type 2 DM, no treatment for DM with ODM or diet, HbA1c >9.5% on ODM, history of CHF, NYHA class III, IV, use of TZDs or other investigational drugs
Maffioli, 2013[111] Italy RCT	Neither year reported 6 Months	Yes	No	Not Extracted/ 170 outpatient care - unclear if specialty or primary care	Age <18 years, HbA1c <8.0%, BMI < 25.0 or >34.9 kg/m2, Prior use of any diabetes treatment, Any kidney disease, History of CVD, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, does not have hepatic steatosis by ultrasound diagnosis, history of ketoacidosis, muscle toxicity, serum creatine phosphokinase values higher than, 2 times the ULN, severe anemia, known contraindications to pioglitazone, glibenclamide, or HMG-CoA inhibitors
Malone, 2005[205] Multinational Europe RCT	Neither year reported 32 Wks	Yes	Yes	97/119 NR	Age <30 or>75 years, HbA1c >2.0 times the upper limit of normal, HbA1c <1.3 times the upper limit of normal, used glitazones within 30 days prior to the study, used NPH QD or BID 30-days prior to entry, expected to benefit from prandial control
Malone, 2003[112] 14 countries not specified randomized, open-label, 2 arm parallel prospective study	Neither year reported 16 Wks	Fewer than 10% of participants were excluded during run-in	Yes	NR/597 subgroup completing test meals	Age < 30 or >75 years, HbA1c <125% of upper limit of normal by local lab within 4 wks prior to entry, BMI >40 kg/m^2, not Type 2 DM, not use of single oral agent (metformin or SU) for 3 months prior to study at max clinically effective dose for previous 30 days

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Malone, 2004[204] US RCT	Neither year reported 32 Wks	Yes	Yes	145/111 NR	Age <30 OR >80 years, HbA1c <1.3 or >2.0 times normal, BMI >40 kg/m^2, HbA1c value that is less than or greater than 1.3 and 2.0 times the ULN within 30 days before the study, while using 1 or more ODM without insulin for 30 or more days before study start
Marre, 2002 [113] Netherlands, Denmark, Portugal, France, Belgium RCT	4 months (Planned duration)	Not extracted	Yes		Age <18 years, any liver disease, any kidney disease, history of CVD, other
Moon, 2014[114] Korea RCT	2007 2009 48 Wks	Yes	Yes	Not Extracted/ 75 NR	Age <18 or >75 yr, HbA1c >12.00% or <7.50%, BMI>=35kg/m2, Any liver disease, Any kidney disease, not on metformin monotherapy (at a dose of >1000mg/day for 3 months prior to enrollment), Taking medications (other than antidiabetic medications) known to affect glycemic control such as glucocorticoids
Nauck, 2007 [118] US, Multinational Europe, Multi-continent RCT	Neither year reported 52 Wks	Yes	Yes	2141/1172 NR	Age <18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15 mmol/L, insulin use within 8 wks of screening, history of Type 1 DM, other treatments for hypoglycemia
Nauck, 2009[119] Multi-continent RCT	Neither year reported 26 Wks	Yes	Yes	Not Extracted/ 527 NR	Age <18 or >80 yr, NbA1c >10.00% or <7.00%, BMI <23 or >45 kg/m2, Any kidney disease, used antidiabetic agents other than met within the 3 months prior to screening, or not on ongoing (>=3 months) stable metformin monotherapy regimen (>=1500mg per day for at least 8 wks), C-PEPTIDE CONCENTRATION <0.26 nmol/l, use of steroids or weight loss meds in last 3 months, after run-in/stabilisation period FPG>=275mg/dl, during run-in/stabilisation peiod <75% compliance with the single-blind placebo regimen h/o cardiac surgery or cardiovascular disease in last 6 months history of cancer (other than squamous cell or basal cell carcinoma of the skin that had not been in full remission for at least 5 years) laser treatment for proliferative diabetic retinopathy within 6 months history of treated diabetic gastroparesis New York Heart

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					Association Class 3 or 4 heart failure
Nauck, 2011[120] Multi-continent RCT	2008 52 Wks	Yes	Yes	Not Extracted/ 814 NR	Age < 18 years, HbA1c >10% or <6.50%, BMI > 45.0 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, not taking metformin +/- another oral antidiabetes drug, FPG > 15 mmol/L; C-peptide < 0.33 nmol/L, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; polyuria/polydipsia with > 10% weight loss, calculated creatinine clearance < 60 mL/min; urine albumin:creatinine ratio > 203.4 mg/mmol, AST and/or ALT and/or creatine kinase >= 3x ULN; serum total bilirubin > 34 micromol/L, Hb <= 11 g/dL for men and <= 10 g/dL for women; abnormal thyroid stimulating hormone level, SBP >= 180 mmHg and/or DBP >= 110 mmHg, cardiovascular event in last 6 months, CHF, significant respiratory, hematological, oncological, endocrine, immunological, and alcohol and/or substance misuse disorders, use of systemic corticosteroids equivalent to >10 mg of oral prednisolone within 30 days of enrolment, history of bariatric surgery; use of weight loss medication within 30 days or enrolment
Nauck, 2014[121] Country NR RCT adaptive, seamless	Neither year reported 52 Wks	Yes	Yes	Not Extracted/ 1098 NR	Age <18 or >75 years, HbA1c >= 9.5%, <8% if on diet and exercise alone or <7% if on OAD monotherapy or combination therapy, BMI <25 or >40 kg/m2, diagnosed <6 months, Prior or current use of insulin, Prior or current use of study drug, unstable weight during the 3-months prior to study entry
Pantalone, 2009[208] United States Prospective or retrospective cohort	Start year: 1998 End year: 2006 8 Years	NA	Yes	NR/20450 Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), on dialysis, on combination ODM, on insulin or other injectible antidiabetics, history of CHF
Pavo, 2003[123] Russia and Hungary RCT	32 wks (Planned duration)	Not extracted	Yes	Not extracted	Age <40 years, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <7.5% or >11.0%, no Type 2 DM, other

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Perez-Monteverde, 2011[124] Country NR RCT	Neither year reported 12 Wks	Yes	Yes	Not Extracted/ 492 NR	Age <18 - >78, HbA1c >12 or <7.5, Contraindication or history of intolerance to metformin, type 1 Diabetes, history of ketoacidosis, symptomatic hyperglycemia, hypersens or contraind to study drug, not taking an antihyperglycaemic agent (AHA) within the previous 3 months and not more than 4 wks cumulatively in the previous 3 year, likely to need a drug that is a CYP2C8 inhib or inducer, symptomatic hyperglycaemia or a site fingerstick glucose < 130 mgГüä dl or > 320 mgГüä dl at the randomisation visit
Perez, 2009 [125] United States, Multinational Europe RCT	Neither year reported 24 Wks	Run-in period but number of participants excluded was NR	Yes	1436/600 NR	Age <18 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), contraindication or history of intolerance to metformin, HbA1c <7.5% or >10%, BMI >45 kg/m^2, pregnant, nursing, triglyceride level 500, if they were NOT discontinued metformin and TZD therapy due to lack of efficacy
Pfutzner, 2011[128] Germany (assumed based on author affiliations RCT	Neither year reported 24 Wks	No	Yes	Not Extracted/ 305 NR	Age <18 - >75, HbA1c <6.5, Any liver disease, Any kidney disease, History of CVD, Pregnant, patients without dyslipidemia, Prior use of any diabetes treatment except for metformin, no current treatment MET, respiratory, neurological or hematlogical disease, not on individually-determined maximal metformin, hypersensitivity to study drugs, history of severe or multiple allergies, h/o significant CVD (greater than NYHA stages II-IV)
Pfutzner, 2011[129] Multi-continent RCT	Neither year reported 76 Wks	Yes	Yes	Not Extracted/ 1306 Community outpatient settings (unspecified)	Age <18 or >77 years, HbA1c >12.00% or <8.00%, BMI >40 kg/m2, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, fasting C-peptide < 1.0 ng/ml, symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, CVD event within the prior 6 months or NYHA stage III/IV congestive heart failure and/or LVEF </= 40%, psychiatric disorder, alcohol or drug abuse within previous year, treatment with potential CYP3A4 inhibitors or inducers, immunocompromised individuals, clinically signficant abnormal hepatic, renal, endocrine, metabolic or hematological screening tests
Pratley,	Start year:	None	Yes	1302/665	Age <18 or >80 years, any liver disease (such as elevated

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
2010 [130] Multi-continent, Europe, USA and Canada RCT	2008 End year: 2009 26 months				aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7.5% or >10%, BMI >45 kg/m^2, no Type 2 DM, cancer, contraindication to trial drugs, recurrent hypoglycemia or hypoglycemia unawareness, not on metformin for at least 3 months, on any non-metformin anti-hypoglycemic in past 3 months
Pratley, 2014[131] Multi-continent RCT	Neither year reported 26 Wks	Yes	Yes	Not Extracted/ 784 NR	Age <18yr or >80 yr, HbA1c >10% or <7.50%, BMI <23 or >45 kg/m2, <20 or >35 kg/m2 for Asian participants, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, Not using adequate contraception, class 3 or 4 CHF OR recent CVD event in last 3 months such as MI, stent, bypass, adequate controlled glycemia following treatment with diet and exercise alone for at least 2 months prior to screening, fasting C-peptide concentration < 0.8ng/ml (0.26nmol/l), lack of ability or willingness to monitor blood glucose using a home glucos monitor and keep a glucose diary, at week-1 of the placebo run-in/stabilization period prior to randomization: HbA1c<7.5% or >10%, at week-1 of the placebo run-in/stabilization period prior to randomization: study drug compliance < 75% or >125%, at week-1 of the placebo run-in/stabilization period prior to randomization: use of oral or systemically injected glucocorticoids or weight-loss drugs, low hemoglobin levels (Γëñ 12 and Γëñ 10 g/dL for men and women, respectively), elevated blood pressure (ΓëÑ 150 and ΓëÑ 90 mm Hg for systolic and diastolic, respectively), hemoglobinopathy;
Qiu, 2014[132] Multi-continent RCT	Neither year reported 22 Wks	Yes	Yes	Not Extracted/ 279 NR	Age <18 or >80, HbA1c >10.5 or <7, Any kidney disease, FPG and/or fasting self-monitored blood glucose, 15.0 mmol/L during the pretreatment phas, diabetic ketoacidosis, history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident) within 3 months before screening, un- controlled hypertension, not on metformin monotherapy at protocol-specified doses (at least 1500 mg/d (>2000 mg/d preferred), on any other diabetes medication within last 12 wks not completing the placebo run-in period
Rajagopalan,		Not	Yes	Not extracted	Age <18 years, any liver disease, no Type 2 DM, other

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
2005[225] US Cohort		extracted			
Raskin, 2007[134] US RCT	Neither year reported 28 Wks	Run-in period but number of participants excluded was NR	NR	N:/NR NR	Age <18 or >75 years, HbA1c ≤8.0%, BMI >40 kg/m^2 or weight >125 kg (275 lbs.), pregnant, nursing, not using adequate contraception, if not on metformin ≥1,000mg /day as a single agent or in ODM combination therapy for at least 3 months before the trial, history of insulin use
Raz, 2008 [188] Multi-continent RCT	Neither year reported 30 Wks	Run-in period but number of participants excluded was NR	Yes	544/190 NR	Age <18 or >78 years, HbA1c <8% after run-in, HbA1c >11% after run-in, BMI <20 or >43 kg/m^2, pregnant, nursing, insulin within 8 wks prior to screening, PPAR-G or incretin mimetics within 12 wks prior to screening, Type 1 DM, FPG <7.2 or >15.6 mmol/L consistently during run-in, no Type 2 DM
Reasner, 2011[135] US RCT	2007 2009 44 Wks	Yes	Yes	Not Extracted/ 1250 NR	Age <18 or >78 years, HbA1c <7.5%, Prior use of any diabetes treatment, Any liver disease, History of CVD, Contraindication or history of intolerance to metformin, No type 2 diabetes, Not on diet/exercise regimen, Finger stick glucose test <7.2 or >17.8 mmol/l, Type 1 diabetes
Ridderstrale, 2014[136] Multi-continent RCT	2010 2011 104 Wks	Yes	Yes	Not Extracted/ 1549 NR	Age <18, HbA1c >10 or <7, BMI >45, Any kidney disease, not on stable dose of MFM IR (>=1500mg/day or max tolerated dose, or max dose according to local label) for at least 12 wks prior to randomization blood glucose concentration greater than 13 3 mmol/L after an overnight fast during the placebo run-in, confi rmed by a second measurement, use of antidiabetes drugs other than metformin immediate release any time during the 12 wks before randomisation
Rigby, 2010 [137] United States, Multi-continent RCT	Start year: 2007 End year: 2008	NA	Yes	169/356 NR	Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >10% (9.5% if on metformin combination therapy), HbA1c <7% (6.5% if on metformin combination therapy), BMI>

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					40 kg/m^2, LDL<50mg/dl or TG ≥500 mg/dL, weight loss program with ongoing weight loss or starting an intensive exercise program within 4 wks of screening, need for oral corticosteroids, bile acid sequestrants, or any antidiabetes medications other than metformin, >2 months insulin, not on metformin for ≥3 months (1500-2550 mg/day), Type 1 DM and/or ketoacidosis, dysphagia/swallowing disorders, intestinal motility disorders, pancreatitis, HIV/AIDS, drug/alcohol abuse within 2 years, any serious disorder including pulmonary, hepatic, gastrointestinal, uncontrolled endocrine/metabolic, hematologic/oncologic (within 5 years), neurologic, or psychiatric diseases, current treatment with TZD/combo with metformin/colesevelam/fixed-dose combination product including metformin, hospitalization within 14 days of screening
Robbins, 2007[138] US, Multinational Europe, Multi-continent, India, Australia RCT	Neither year reported 24 Wks	Run-in period but number of participants excluded was NR	NR	433/317 NR	Age <35 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <6.5% or >11%, pregnant, nursing, not using adequate contraception, patients who were receiving continuous SC insulin injections or a total daily insulin of >2.0 U/kg or who had a change in type or dose of lipid-altering medications or TZD use up to 3 months before the study, fasting triglyceride level >4.5 mmol/L, serum creatinine >134 micromol/L (men) or >109 micromol/L (women)
Roden, 2013[139] Multi-continent RCT	2010 2012 24 Wks	Yes	Yes	Not Extracted/ 899 Inpatient/hospital Outpatient: primary care Outpatient: subspecialty care setting academic medical ctrs, hospitals, and private practices	Age <18, <20 in Japan, <18 or >65 in India, 10 or 9 in Germany, HbA1c <7, BMI >45, Any kidney disease, diabetes treatment in 12 wks before randomization, uncontrolled hyperglycaemia (glucose concentration >13 mmol/L after an overnight fast during the placebo run-in phase and confirmed by a second measurement),, contraindications to sitagliptin according to the local label, treatment with antiobesity drugs within 3 months before informed consent, treatment with systemic steroids at time of informed consent, change in dose of thyroid hormones within 6 wks before informed consent,, any uncontrolled endocrine disorder apart from type 2 diabetes. did not meet inclusion criteria after placebo run-in
Rosenstock, 2006[140]	Start year: 2003 to	Yes	Yes	1252/468	Age <18 or >70 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
	2004			multicenter	as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or > 11%, FPG >15mmol/l, hematological disease, uncontrolled hypertension while on antihypertensive treatment, intermittent or chronic use of oral or intravenous corticosteroids, investigators discretion, use of investigational agent within 30 days of the study (or five half lives of the investigational drug if longer than 30 days), previous history of severe edema or medically serious fluid related event associated with TZD, acute or chronic metabolic acidosis, history of diabetic ketoacidosis
Multi-continent RCT	32 Wks				
Rosenstock, 2010[141]	Neither year reported	Yes	Yes	Not Extracted/ 655	Age <18 or >80yr, HbA1c >11% or <7.50%, BMI <23 or >45 kg/m2, not drug-naive (current antihyperglycemmic medication or >6 days of any such agent within 3 months of screening), successful glycemic control with diet and exercise for >=2 months prior to screening
Country NR RCT	26 Wks			NR	
Rosenstock, 2012[142]	Neither year reported	No	Yes	Not Extracted/ 451	Age <18, >65, HbA1c >10.50% or <7, unstable weight or BMI <25 or >45 kg/m^2 (<24 or >45 kg/m^2 for Asians), Diagnosed with type 2 diabetes for less than 3 months, On metformin monotherapy dose <1500mg/day, On metformin monotherapy for less than 3 months, Serum creatinine >1.5mg/dl for men and >1.4 mg/dl for women
Multi-continent RCT	12 Wks			NR	
Rosenstock, 2013[143]	Neither year reported	Yes	Yes	Not Extracted/ 441	Age <65 or >90 yr, HbA1c >9.0% for patients on diet and exercise therapy alone, 8.0% for patients on oral antidiabetic monotherapy & 9.0% after washout period without medications within 2 wks 6.50% not able or unwilling to self-monitor blood glucose with a home glucose monitor
Multi-continent RCT	52 Wks			NR	
Rosenstock, 2013[144]	Neither year reported	Yes	Yes	Not Extracted/ 495	Age <18 or >80, HbA1c >9 if on MFM and one other OAD or >10 if on MFM monotherapy, 6.5 if on MFM and one other OAD, <7 if on MFM monotherapy, BMI >40, Any liver disease, Any kidney disease, prior treatment that didn't include MFM and one other oral OAD, unchanged antidiabetic therapy for <10 wks prior to screening including stable metformin therapy (ГёÑ1500 mg/day or maximum tolerated dose);, diseases of the central nervous system; chronic or clinically relevant acute infections; history of clinically relevant allergy/hypersensitivity;,
Multi-continent RCT	12 Wks			NR	

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months., h/o of MI, CVA, or TIA in past 6 mo, HbA1c <7 or >10 at start of placebo run-in, history of clinically relevant allergy/hypersensitivity, treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months
Rosenstock, 2015[145] Multi-continent RCT	2012 2014 24 wks	Yes	Yes	NR/534 NR	No type 2 diabetes. On stable metformin therapy (>/=1,500 mg/day) for >=8 weeks before screening. Have Cpeptide concentrations >/=1.0 ng/mL. Uncontrolled hypertension (systolic blood pressure >/=160 mmHg and diastolic blood pressure >/=100 mmHg) at randomization. Fasting plasma glucose (FPG) >/=270 mg/dL during the 4-week lead-in period. Cardiovascular disease within 3 months of screening, congestive heart failure (New York Heart Association functional class IV). Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 or serum creatinine >/=1.5 mg/dL in men or >/=1.4 mg/dL in women. Patients who received any antidiabetic medication, other than metformin, for more than 14 days during the 12 weeks before screening.
Ross, 2012[146] Multi-continent RCT	2009 2010 12 Wks	Yes	Yes	Not Extracted/ 491 NR	Age <18 or > 80yr, HbA1c >10.0% when taking met alone; 9.5% when taking met and no more than one other oral antidiabetic drug (SU, meglitinide, DPP-4 inhibitor or a-glucosidase inhibitor with unchanged dose for 12 wks prior to informed consent); 10% after the placebo run-in for 7.00%, BMI > 45kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, total daily dosage of met was not >=1500mg/day or maximum tolerated dose b.i.d., or was on unstable dose (changed within 12 wks prior to randomisation or during the study), treatment within the prevous 3 months with a thiazolidinedione, a GLP-1 receptor agonist, or an antiobesity drug, major cvd event in last 6 months
Russell-Jones, 2012[147] Multi-continent RCT	2008 2010 36 Wks	No	Yes	Not Extracted/ 820 NR	Adults, HbA1c >11 or <7.1, BMI <23 - >45, Prior use of any diabetes treatment, unstable weight
Schernthaner, 2015[148]	2009 2012	Yes	Yes	NR/720 NR	Age <65, HbA1c>9, HbA1c7, any liver disease, any kidney disease, type 1 diabetes, any antihyperglycaemic therapy other than metformin <8 wks before enrollment, glucocorticoids, cytochrome P450 3A4 inducers,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Multi-continent RCT	52 wks				history of ketoacidosis or hyperosmolar non-ketonic coma, haemoglobinpathies, cognitive function problems, alcohol or illegal drug abuse
Schernthaner, 2004[149] Europe RCT	12 months (Planned duration)	Not extracted	No	Not extracted	Age <35 or >75 years, treatment experienced, HbA1c <7.5% or >11%, no Type 2 DM
Schumm-Draeger, 2015[151] Multi-continent RCT	2010 2011 20 wks	Yes	Yes	NR/400 NR	Not on stable dose of MET >=1500mg/day for >= 10 weeks. Weight loss (sx of uncontrolled dm). Recent cardiovascular event or New York Heart Association class III or IV congestive heart failure. BP>=160/100. Clinically significant haematological or oncological conditions. Symptoms of poorly-controlled diabetes.
Scott, 2008[153] Multi-continent RCT	Neither year reported 18 Wks	Run-in period but number of participants excluded was NR	Yes	486/273 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >11%, not on 10 wks on stable dose of metformin, insulin use, Type 1 DM, glucose > 270 mg/dL
Scott, 2007[152] US RCT	Neither year reported 12 Wks	Run-in period but number of participants excluded was NR	Yes	2186/743 NR	Age <21 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), Type 1 DM, gall bladder disease, elevated CK
Seck, 2010 [154] NR RCT	Neither year reported 2 Years	Run-in period but number of participants excluded was NR	Yes	2141/1172 NR	Age <17 years or >78 years
Seino, 2010[155]	Neither year reported	Yes	Yes	NR/464 NR	Age <20 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Japan RCT	24 Wks				creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, HbA1c <7% or >10%, BMI >35 kg/m^2, treated with insulin within 12 wks of the start of the study, receiving or expecting to receive systemic corticosteroids, known hypoglycemia unawareness or recurrent major hypoglycemia unawareness or reccurent major hypoglycemia, no Type 2 DM, treated with diet therapy for less than 8 wks, on more than 1/2 of the recommended maximum dose of an SU (e.g., on more than 2.5 mg of glibenclamide)
Seino, 2012[156] Japan RCT	2008 2009 12 Wks	Yes	Yes	Not Extracted/ 288 outpatient, but not specified	Age <20 or >=65years, HbA1c >=10.4% after 8 wks of observation, 6.9% after 8 wks of observation, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, >=10% variation in A1c between week 4 and 8, not receiving metformin at a stable dosage for at least 12 wks plus specific dietary and exercise therapies, administration of any investigational drug, orhter than met, within 12 wks of study initiation, a history/symptoms of lactic acidosis h/o drug abuse/dependency, severe cardiovascular or pulmonary function impairment or severe pancreatic, cerebrovascular, or hematologic diseases, dehydration, gastrointestinal disorders, malignant tumours, elevated blood pressure (>=180 / 110mmHg
Shihara, 2011[157] Japan RCT	2007 2010 6 Months	No	No	Not Extracted/ 191 NR	Age <30 - >75, HbA1c >=10.4 <6.9, Prior or current use of study drug, Any liver disease, Any kidney disease, History of CVD, CHF, Any hematological condition, Any pancreas condition, not committed to stable diet & exercise regimen, use of any dim med in past month, capable of reading consent form
Skrivanek, 2014[226] Country NR RCT	Neither year reported Not applicable	Yes	Yes	Not Extracted/ 230 NR	Age <18 or >75 years, HbA1c >9.50, <8.0% if on diet and exercise alone and <7.0% if on OAD monotherapy or combination therapy, BMI <25 or >40 kg/m2, diagnosed <6 months
Srivastava, 2012[158] India RCT	2008 2009 18 Wks	No	NR	Not Extracted/ 50 Outpatient (not specified if PC or	Age <=18, HbA1c >=10 of <=7, Any liver disease, Any kidney disease, History of CVD, not on metformin monotherapy for at least 3 mo, type 1 diabetes, other terminal illness

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
				subsp)	
St John Sutton, 2002[159] US RCT	52 wks (Planned duration)	Not extracted	Yes	Not extracted	Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, no type 2 DM, other
Stenlof, 2014[213] Country NR RCT	Neither year reported 52 Wks	Yes	Yes	Not Extracted/ 587 NR	Age <18 or >80, HbA1c >10 or <7, Prior or current use of study drug, Any kidney disease, if on AHA other than PPAR agonist or combination MFM+SU, FPG >15 mmol/l, h/o type 1 dm history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident) within 3 months before screening
Stewart, 2006[160] Multinational Europe RCT	Start year: 2003 to 2004 32 Wks	Yes	Yes	1397/526 NR	Age <18 or >70 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >9%, drug naive patients with FPG <7 mmol/l or >9mmol/l, patient on monotherapy with FPG < 6.0mmol/l or >8 mmol/l, prior history of exposure to TZDs within previous 6 months, use of insulin anytime in the past, uncontrolled hypertension
Tan, 2004 [162] Denmark, Finland, Norway, and Sweden. RCT	52 wks (Planned duration)	Not extracted	Yes	Not extracted	Treatment experienced, HbA1c <7.5% or >11% for patients not receiving ODM, <7.5% or > 9.5% for patients receiving ODM, no Type 2 DM, other
Taskinen, 2011[164] Multi-continent RCT	Neither year reported 24 Wks	Yes	Yes	Not Extracted/ 701 NR	Age <18 or >80 years at screening, HbA1c >10.0% for met mono patients, 9.0% for patients treated with an additional medication; by the start of the placebo run-in, 10.0% for all patients at screening, 7.0% for met mono patients, 6.5% for patients treated with an additional medication; by the start of the placebo run-in, 7.0% for all patients, BMI >40 kg/m2, Any liver disease, Any kidney disease, not receiving met at a dose of >=1500mg/day (or max tolerated dose), more than one other oral antidiabetes medication, antidiabetes medications have changed within 10 wks prior to the date of informed consent or the dose of met was not stable for >=12 wks before randomization, treated with rosiglitazone,

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
					pioglitazone, a GLP-1 analogue, insulin or antiobesity drug within 3 months, changed dosage of thyroid hormone treatment within 6 wks or were being treated with systemic steroids at the date of informed consent, acute or chronic metabolic acidosis, hereditary galactose intolerance, dehydration, have participated in another trial of an investigational drug within the previous 2 months, acute MI, stroke, or TIA within last 6 months or acute or unstable CHF
Tosi, 2003 [167] Italy RCT, cross-over	6 months (Planned duration)	Not extracted	Yes	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.3%, no Type 2 DM, other
Umpierrez, 2006[170] US RCT	Neither year reported 28 Wks	Run-in period but number of participants excluded was NR	Yes	538/210 Outpatient: primary care, Outpatient: subspecialty care setting	Age <18 or >79 years, HbA1c <7.5% or >10%, BMI <24 kg/m^2, diagnosis of Type 2 DM <6 months, no taking stable doses of metformin (1-2.5g/day) or extended-release metformin (0.5 -2.0g/day) as their only ODM for at least 2 months prior to the study, C-peptide <0.27nmol/L, subjects treated with insulin, TZDs or SU within 3 months prior to study enrollment, history of substance abuse, severe hypoglycemia, acute metabolic complications, clinically significant abnormal baseline laboratory values including hematology, blood chemistry or urinalysis
Umpierrez, 2014[171] Multi-continent RCT	2010 2012 52 Wks	Yes	Yes	Not Extracted/ NR NR	Age <18 years, HbA1c >9.50% or <6.50, <3 months or >5 years, Prior or current use of insulin, Prior or current use of study drug, on more than one oral antihyperglycemic medication(OAM) or on one OAM for <3 months prior to screening., receiving an OAM and taking >50% of the approved maximum daily dose per respective labels in participating countries, have been taking thiazolidinediones or GLP-1 receptor agonists during the 3 months prior to screening, on one oral medication < 3 months
van der Meer, 2009[172] Netherlands RCT	Neither year reported 24 Wks	Fewer than 10% of participants were excluded during run-in	Yes	173/80 NR	Age <45 or >65 years, female, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >8.5%, BMI <25 kg/m^2 or >32 kg/m^2, SBP <150 mm Hg, DBP <85 mm Hg, prior TZD or insulin use

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
Wang, 2015[173] China-Philippines-Malaysia RCT	2010 2012 24 wks	Yes	Yes	NR/306 NR	Age <18 & >80, HbA1c>10, HbA1c7, BMI >45, prior or current use of insulin, prior or current use of study drug, any liver disease, any kidney disease, history of CVD, confirmed hyperglycemia (glucose 240 mg/dL after overnight fast during wash-out or run-in), current treatment with a TZD, insulin, GLP-1 agonist, DPP-4 inhibitor, or antiobesity drug, alcohol or drug abuse, steroids use,
Weir, 2011[227] Canada Retrospective cohort	1997 2008 Not applicable	Not applicable	No	Not Extracted/ 2650 Administrative database	Age <66, no treatment for diabetes for at least 1 year, no SCr measurement available between 2002-2008, no use of a dm2 medication in the 120 days prior to the case's index date Ontario resident
Weissman, 2005[174] US RCT	Neither year reported 24 wks (Planned duration)	Run-in period but number of participants excluded was NR	Yes	1270/766 NR	Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >8.5% for subjects having received prior combination treatment (metformin + SU), HbA1c < 7% or > 10% for drug naive or prior monotherapy subjects, BMI <27 kg/m2, FPG < 126mg/dL or >270mg/dL, anemia, severe edema, prior insulin use within 3 months of study start, non-compliant patient with metformin up-titration
White, 2014[175] Multi-continent RCT	2009 2010 12 Wks	Yes	Yes	Not Extracted/ 160 outpatient	Age <18 and >78 years, HbA1c >10% or <7%, BMI >45, Pregnant, Nursing, not on metformin monotherapy at >=1500 mg for >=8 wks prior to study start, marked polydipsia and polyuria and >10% weight loss<3 months before screening, h/o DKA or HHNC or insulin use in the last year, h/o CVD within 3 months of screening, CHF class 3 or 4 or known EF<=40%, h/o hemoglobinopathies
Williams-Herman, 2009[176] NR RCT	Neither year reported 54 Wks	Run-in period but number of participants excluded was NR	Yes	3544/1091 NR	Age <18 or >78 years, HbA1c ≤7.5% or ≥11% after screening diet/exercise run-in (which included a wash-out period), lack of adequate compliance (≥75% by tablet count) during 2-week single-blind placebo run-in period, no Type 2 DM
Williams-Herman,	Neither year reported	Yes	Yes	Not Extracted/ 1091	Age <18 or >78 years, HbA1c >11% or <7.50%, Any liver disease, Any kidney disease, History of CVD, completed the 54-week base study, >/=

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
2010[177] Multi-continent RCT	104 Wks			NR	75% compliant in taking study medication, had not developed contraindication to study medication
Wright, 2006 [228] UK RCT	Start year: 1977 End year: 1991 6 Years	Fewer than 10% of participants were excluded during run-in	Yes	7616/4191 23 clinical Center	Age <25 or >65 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG ≤6 mmol/l x2 after being diagnosed with diabetes, ketonuria> 3 mmol/l, mixed ethnicity, severe previous illness that would limit life expectancy or require systemic treatment, serum creatinine>175 umol/l, if on same treatment for <6 years
Xu, 2015[178] China RCT	2010 2012	No	Yes	NR/416 NR	Acute or severe chronic diabetic complications or illnesses (ketoacidosis, hyperosmotic state, lactic acidosis, severe microand macro-vascular complications, and hepatic dysfunction). Presence of glutamic acid decarboxylase antibodies. Use of drugs affecting gastrointestinal motility, weight and glycaemia. History of pancreatitis. Triglyceride (TG) levels ГëÑ5 mmolL-1. Body weight not atble over the last 3 months.
Yamanouchi, 2005[179] Japan RCT	12 months (Planned duration)	Not extracted	No	Not extracted	Any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, retinopathy, HbA1c <7.0%, no Type 2 DM, other
Yang, 2011[180] Multinational Asia (China - India - SouthKorea RCT	Neither year reported 24 Wks	Yes	Yes	Not Extracted/ 570 NR	Age <18, HbA1c >10 or >7, Any liver disease, Any kidney disease, Pregnant, Nursing, not on stable dose of metformin; C-peptide <0.33 nmol/l, history of diabetic ketoacidosis or hyperosmolar coma, symptoms of poorly controlled dm, CHF - NYHA III-IV, use of sysetmic steroids or CYP 3A4 inducers Hemoglobinopathies, signiifcant cardiovasc illness within 6 mo of enrollment, autoimmune skin d/o, GI surgery that could affect absorpotion, immunocompromised, drug or alcohol abuse in past 12 mo, abnormal lab, exam, ECG that would compromise safe, successful participation - investigator discretion, insulin in past yr, Prior use of any diabetes treatment besides metformin within 8 wks, ever used DPP4 inhib
Yang, 2011[181] Asia - Korea,	Neither year reported	Yes	Yes	Not Extracted/ 929	Age <18 and >80 years, HbA1c >11% for subjects onOAD monotherapy and 10% for subjects onOAD combination therapy 7%, BMI >45kg/m2, not treated with one or more oral antidiabetic drugs

Author, year Country Study design	Enrollment period Follow-up duration	Run-in period	Industry support	Number screened/ enrolled Source population	Exclusion criteria
China, India RCT	16 Wks			NR	(OADs) for at least 3 months, treated with insulin within the last 3 months, after run-in with up-titration of metformin to 2000 mg/day and 3-wk maint at that dose, subj with FG 7-12.8 mmol/l could be ranodomized
Yang, 2012[182] China RCT	2009 2010 24 Wks	Yes	Yes	Not Extracted/ 395 NR	Age <18 - >78, HbA1c >11 or <7.5, Any liver disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Diabetes type 1, history of ketoacidosis, CHF, unstable CHD, not Chinese, able to get off other diabetes meds during run-in, prior use of TZDs
Yoon, 2011[183] Korea RCT	2007 2008 48 Wks	Yes	Yes	Not Extracted/ 349 NR	Age <30 - >65, HbA1c >9.5 or <6.5, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, history of lactic acidosis glucocorticoid users, contraind to SU
Yuan, 2012[184] China RCT	Neither year reported 26 Wks	No	NR	Not Extracted/ 59 NR	Age <=18yr. HbA1c >10% or <7%, BMI <=28 or >=40kg/m2, diagnosis>=1months, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, waist circumstance <=90cm for male or <85cm for female (could be excluded if did not meet this OR the BMI criteria), have ever been treated with lipd lowering agents, blood pressure > 150/100mmHg, clinically suspected hyper- or hypothyroid disease and Cushing syndrome

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = NR; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table D11. Population characteristics of studies evaluating safety of diabetes medications

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Seino, 2010[155]	Glibenclamide, 132	58.5	65	Asian: 100	24.4 NR	8.978	8.5	12
	Liraglutide, 268	58.2	68	NR	24.5 NR	8.92	8.1	22
DeFronzo, 2005[28]	Metformin + placebo, 113	54	NR	NR	34 100	8.2	6.6	NR
	Metformin + exenatide, 110	53	NR	NR	34 100	8.3	6.2	NR
	Metformin + exenatide, 113	52	NR	NR	34 101	8.2	4.9	NR
Rosenstock, 2015[145]	Metformin + saxagliptin + placebo, 176	55	NR	NR	31.8 NR	9.03	8.2	NR
	Metformin + dapagliflozin + placebo, 179	54	NR	NR	31.5 NR	8.87	7.4	NR
Xu, 2015[178]	Pioglitazone, 136	NR	51.5	NR	NR 70.6	8	NR	18
	Exenatide, 142	NR	55.1	NR	NR 71.7	8	NR	32
Del Prato, 2014[33]	Metformin + glipizide, 874	55.4	50.5	Caucasian: 61 African American: 9.3 Asian: 23.2 Other: 6.5	31.1 85.6	7.71	5.45	NR
	Metformin + alogliptin, 880	55.2	47.6	Caucasian: 63.3 African American: 8.4 Asian: 21.7 Other: 6.5	31.3 85.3	7.78	5.12	NR
	Metformin + alogliptin, 885	55.5	51.1	Caucasian: 62.7 African American: 7.5 Asian: 66 Other: 6.4	31.3 86.3	7.94	5.53	NR
Schumm-Draeger,	Metformin + placebo, 101	58.5	46.5	NR	31.74 NR	7.94	5.53	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
2015[151]	Metformin + dapagliflozin 5mg, 100	55.3	46.5	NR	33.09 NR	7.78	5.12	NR
	Metformin + dapagliflozin 10mg, 99	58.5	49.5	NR	32.25 NR	7.71	5.45	NR
Derosa, 2010[39]	Metformin + glibenclamide, 65	56	51	NR	28.5 NR	8.9	NR	8
	Metformin + exenatide, 63	57	48	NR	28.7 NR	8.8	NR	4
Defronzo, 2010[30]	Metformin + rosiglitazone, 45	NR	NR	NR	NR NR	7.9	NR	11
	Metformin + exenatide, 45	NR	NR	NR	NR NR	7.8	NR	12
Del Prato, 2015[32]	Metformin + glipizide, 401	58.6	54.9	NR	NR 87.6	7.74	6.6	NR
	Metformin + dapagliflozin, 400	58.1	55.3	NR	NR 88.4	7.69	6.1	NR
Aschner, 2010[7]	Metformin, 439	55.7	44	NR	30.9 NR	7.2	2.1	75
	Sitagliptin, 455	56.3	48	NR	30.7 NR	7.2	2.6	61
Seck, 2010[154]	Metformin + sitagliptin, 248	57.6	57.3	AA: 3.6, Asian: 9.3, C: 77.4, H: 5.6, O: 4	30.9 88.5 kg	7.3	5.8	231
	Metformin + glipizide, 584	57	62.9	AA: 5.1, Asian: 8.2, C: 78.5, H: 5.1, O: 3.1	31.3 90.3 kg	7.3	5.7	328
Komajda, 2010[222]	Metformin + rosiglitazone, 2220	NR	NR	NR	NR NR	NR	NR	NR
	Metformin + sulfonylurea, 2227	NR	NR	NR	NR NR	NR	NR	NR
Pratley, 2010[130]	Metformin + sitagliptin, 219	55	55	AA: 5, Asian: 1, C: 91, H: 16, O: 4	32.6 93.1 kg	8.5	6.3	25
	Metformin + liraglutide, 221	55.9	52	AA: 10, Asian: 3, C: 82, H: 17, O: 5	32.6 93.7 kg	8.4	6	27
	Metformin + liraglutide, 221	55	52	AA: 7, Asian: 2, C: 87, H: 15, O: 4	33.1 94.6 kg	8.4	6.4	52

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Derosa, 2009[38]	Metformin, 67	55	51	C: 100	27.2 77.7 kg	9.1	NR	7
	Metformin + glimepiride, 66	57.7	48	C: 100	27.1 77.4 kg	9	NR	6
	Metformin + pioglitazone, 69	57	49	C: 100	27.4 76.4	9.3	NR	9
	Pioglitazone, 69	54	46	C: 100	27.5 76.7 kg	9.2	NR	9
van der Meer, 2009[172]	Metformin + glimepiride, 39	56.4	100	NR	29.3 NR	7	3	2
	Pioglitazone + glimepiride, 39	56.8	100	NR	28.2 NR	7.1	4	5
Kaku, 2009[98]	Metformin, 86	53	57	NR	25.4 NR	7.55	5.6	7
	Metformin + pioglitazone, 83	52	66	NR	25.6 NR	7.58	4.5	9
Williams-Herman, 2009[176]	Metformin, 182	54.2	45	NR	32 NR	8.5	4.1	46
	Metformin, 182	53.7	48	NR	32 NR	8.7	4.1	56
	Metformin + sitagliptin, 182	53.6	41	NR	32 NR	8.7	4.6	41
	Metformin + sitagliptin, 190	53.7	53	NR	32 NR	8.8	4.1	42
	Sitagliptin, 179	53.5	52	NR	31 NR	8.7	3.9	57
Pantalone, 2009[208]	Rosiglitazone, 1079	61.4	45.5	C: 86.8, Non-Caucasian: 13.2	32.7 NR	7.3	NR	NR
	Any in the SU class, 7427	66.1	49.5	C: 78, Non-Caucasian: 22	31.1 NR	7.6	NR	NR
	Pioglitazone, 1508	61.6	48.3	C: 83.5, Non-Caucasian: 16.5	33 NR	7.3	NR	NR
	Metformin, 10436	56.8	41.8	C: 76.9, Non-Caucasian: 23.1	33.8 NR	7.7	NR	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Hsiao, 2009[215]	Metformin, 46444	59	48.22	NR	NR NR	NR	NR	NR
	Rosiglitazone, 2093	61.24	53.46	NR	NR NR	NR	NR	NR
	Pioglitazone, 495	60.75	52.02	NR	NR NR	NR	NR	NR
	Any in the SU class, 97651	60.71	54.1	NR	NR NR	NR	NR	NR
	Metformin + sulfonylurea, 267754	57.17	54.45	NR	NR NR	NR	NR	NR
	Metformin + rosiglitazone, 2408	57.3	49.8	NR	NR NR	NR	NR	NR
Perez, 2009[125]	Metformin, 210	53.7	46.7	AA: 6.7, Asian: 2.4, C: 88.1, H: 26.2	30.8 NR	8.65	NR	68
	Metformin + pioglitazone, 201	54.7	44.8	AA: 6, Asian: 1.5, C: 91.5, H: 24.4	30.8 NR	8.89	NR	44
	Pioglitazone, 189	54	34.9	AA: 6.9, Asian: 2.6, C: 87.3, H: 25.9	31.2 NR	8.69	NR	64
Rigby, 2009[137]	Metformin + rosiglitazone, 56	54.7	41	AA: 3.6, Asian: 0, C: 28.6, H: 67.9, O: 0	NR 81.1 kg	8.06	7.57	5
	Metformin + sitagliptin, 56	54.8	35.7	AA: 1.8, Asian: 0, C: 23.2, H: 73.2, unspecified: 1.8	NR 79.6 kg	8.17	8.35	11
Dormuth, 2009[219]	THIAZOLIDINEDIONE, 10476	56	48	NR NR	NR NR	NR	4.6	NR
	Rosiglitazone, 6880	56	48	NR NR	NR NR	NR	4.6	NR
	Pioglitazone, 3596	57	48	NR NR	NR NR	NR	4.7	NR
	Any in the SU class, 73863	60	47	NR NR	NR NR	NR	4	NR
Jadzinsky,	Metformin + saxagliptin, 320	52.4	51.6	AA: 2.2, Asian: 15.9, C: 76.9, O: 5	29.9 NR	9.4	2	58

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
2009[91]	Metformin + saxagliptin, 323	52.1	45.2	AA: 2.2, Asian: 16.7, C: 75.2, O: 5.9	30.3 NR	9.5	1.4	62
	Metformin, 328	51.8	49.7	AA: 1.2, Asian: 15.9, C: 76.5, O: 6.4	30.2 NR	9.4	1.7	85
	Saxagliptin, 335	52	50.4	AA: 1.8, Asian: 16.7, C: 76.1, O: 5.4	30.2 NR	9.6	1.7	110
DeFronzo, 2009[29]	Metformin + saxagliptin, 192	54.7	43.2	AA: 3.9, Asian: 4.2, C: 79.7, O: 12	31.7 86 kg	8.1	6.7	44
	Metformin + saxagliptin, 191	54.7	53.9	AA: 5.8, Asian: 1.6, C: 83.2, O: 9.4	31.2 87.3 kg	8.1	6.4	48
	Metformin + saxagliptin, 181	54.2	52.5	AA: 7.7, Asian: 2.8, C: 79.6, O: 9.9	31.1 87.8 kg	8.0	6.3	41
	Metformin, 179	54.8	53.6	AA: 3.9, Asian: 2.2, C: 83.8, O: 10.1	31.6 87.1 kg	8.1	6.7	40
Bunck, 2009[229]	Metformin + exenatide, 36	58.4	63.9	NR	30.9 90.6 kg	7.6	5.7	6
	Metformin + glargine, 33	58.3	66.7	NR	30.1 92.4 kg	7.4	4	3
Garber, 2009[66]	Glimepiride, 248	53.4	54	AA: 12, Asian: 4, C: 77, H: 38, O: 7	33.2 93.4 kg	8.4	5.6	96
	Liraglutide, 247	52	49	AA: 12, Asian: 6, C: 75, H: 35, O: 7	32.8 92.8 kg	8.3	5.3	74
	Liraglutide, 251	53.7	47	AA: 14, Asian: 2, C: 80, H: 32, O: 5	33.2 92.5 kg	8.3	5.2	NR
Kahn, 2008[220]	Glyburide, 1441	NR	58	NR	NR NR	NR	NR	0
	Metformin, 1454	NR	59.4	NR	NR NR	NR	NR	0
	Rosiglitazone, 1456	NR	56	NR	NR NR	NR	NR	0
Scott, 2008[153]	Metformin, 92	55.3	59	Asian: 39, C: 61	30 84.6 kg	7.7	5.4	9
	Metformin + rosiglitazone, 87	54.8	63	Asian: 38, C: 59, O: 3	30.4 84.9 kg	7.7	4.6	2

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + sitagliptin, 94	55.2	55	Asian: 38, C: 61, O: 1	30.3 83.1	7.8	4.9	9
Raz, 2008[188]	Metformin, 94	56.1 (36 to 77)	41	AA: 1, C: 47, H: 25, multiracial: 25, not specified: 2	30.4 81.2 kg	9.1	7.3	16
	Metformin + sitagliptin, 96	53.6 (29 to 73)	51	AA: 3, C: 42, H: 32, multiracial: 22, not specified: 1	30.1 81.5 kg	9.3	8.4	18
Robbins, 2007[138]	Metformin + glargine, 159	58.1	49.4	AA: 5.7, Asian: 14.6, C: 63.3, H: 16.4	32 88.1kg	7.8	12.5	22
	Metformin + insulin lispro 50/50, 158	57.4	50.3	AA: 5.7, Asian: 14, C: 65, H: 15.3	32.1 89.1kg	7.8	11.3	15
Hamann, 2008[80]	Metformin + rosiglitazone, 294	58.5	53	C: 94	33 91.4kg	8	6.3	61
	Metformin + sulfonylurea, 302	59.3	52	C: 95	32.2 88.9kg	8	6.4	71
Chien, 2007[24]	Glyburide, 25	63	53	NR	25.3 63.7 kg	8.69	8.6	6
	Metformin, 25	59	41	NR	25.7 65.6 kg	8.88	6.4	8
	Metformin + glyburide, 26	60	71	NR	24.2 63.8 kg	8.71	9	5
	Metformin + glyburide, 26	57	62	NR	24.2 61.3 kg	8.85	6.6	5
Comaschi, 2007[25]	Metformin + pioglitazone, 103	57	45.63	NR	32.2 85.8 kg	8.4	NR	27
	Metformin + sulfonylurea, 80	59.9	55	NR	29.9 81.9 kg	8.6	NR	13

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Goldstein, 2007[72]	Metformin, 182	53.4	48.9	AA: 6.6, Asian: 7.7, C: 47.8, H: 30.2, not specified: 7.7	32.1 NR	8.9	4.5	29
	Metformin, 182	53.2	45.1	AA: 4.9, Asian: 5.5, C: 58.2, H: 21.4, not specified: 9.9	32.2 NR	8.7	4.4NR	182
	Metformin + sitagliptin, 182	53.3	42.3	AA: 7.7, Asian: 6, C: 52.2, H: 26.9, not specified: 7.1	32.4 NR	8.7	4.4	18
	Metformin + sitagliptin, 190	54.1	55.3	AA: 6.8, Asian: 4.7, C: 53.7, H: 28.9, not specified: 5.8	32.1 NR	8.8	4.5	26
	Sitagliptin, 179	53.3	52	AA: 6.1, Asian: 3.4, C: 52, H: 29.1, not specified: 9.5	31.2 NR	8.9	4.4	37
Davies, 2007[26]	Metformin + NPH, 29	57.9	48.28	AA: 0, Asian: 21, C: 66	32.6 90.4kg	10	7.3	5
	Metformin + BHI 70/30, 27	57.4	80	AA: 4, Asian: 22, C: 70	30.2 82.2 kg	9	9.1	0
Nauck, 2007[118]	Metformin + glipizide, 584	56.6	61.3	AA: 6, Asian: 8.4, C: 74.3, H: 7.9, O: 3.4	31.3 89.7 kg	7.6	6.2	172
	Metformin + sitagliptin, 588	56.8	57.1	AA: 7, Asian: 8.5, C: 73.5, H: 7.3, O: 3.7	NR NR	7.7	6.5	202
Raskin, 2007[134]	Metformin + aspart 70/30, 79	52	52	AA: 13, Asian: 3, C: 52, H: 32, O: 1	31.2 88.7 kg	9.9	NR	12
	Metformin + glargine, 78	51.7	54	AA: 15, Asian: 4, C: 47, H: 32, O: 1	30.8 86.2 kg	9.9	NR	6
Hanefeld, 2007[82]	Glibenclamide, 203	60.1	70	AA: 0, C: 99, O: <1	28.7 NR	8.2	6.4	13
	Rosiglitazone, 189	60.6	58	AA: 0, C: 97, O: 3	28.8 NR	8.2	6	9
	Rosiglitazone, 195	60.4	68	AA: 0, C: 98, O: 2	28.7 NR	8.1	5.9	12

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Scott, 2007[152]	Glipizide, 123	54.7 (21 to 76)	56.9	AA: 3.3, Asian: 4.9, C: 61, O: 24.4, Multiracial: 6.5	30.6 NR	7.9	4.7	23
	Sitagliptin, 123	56.2 (34 to 75)	48	AA: 4.9, Asian: 4.9, C: 63.4, multiracial: 5.7, O: 21.1	30.5 NR	7.9	4.9	7
	Sitagliptin, 123	55.6 (34 to 76)	57.7	AA: 8.9, Asian: 4.9, C: 61, Multiracial: 6.5, O: 18.7	31.4 NR	7.9	5	15
	Sitagliptin, 124	55.1 (28 to 75)	52.4	AA: 4.8, Asian: 2.4, C: 69.4, Multiracial: 7.3, O: 16.1	30.4 NR	7.8	4.2	12
	Sitagliptin, 125	55.1 (30 to 76)	62 49.6	AA: 6.4, Asian: 5.6, C: 68.8, multiracial: 6.4, O: 12.8	30.8 NR	7.9	4.3	18
Kahn, 2006[97]	Glyburide, 1441	56.4	58	AA: 4.2, Asian: 2.2, C: 89, H: 4.2, O: 0.3	32.2 92 kg	7.35	(<1: 44, 1-2: 52, >2: 4)	634
	Metformin, 1454	57.9	59.4	AA: 3.7, Asian: 2.4, C: 89.1, H: 3.8, O: 1	32.1 91.6 kg	7.36	(<1: 46, 1-2: 50, >2: 4)	551
	Rosiglitazone, 1456	56.3	55.7	AA: 4.2, Asian: 2.7, C: 87.2, H: 5.2, O: 0.7	32.2 91.5 kg	7.36	(<1: 45, 1-2: 52, >2: 3)	539
Charbonnel, 2006[21]	Metformin, 237	54.7	59.5	AA: 5.9, Asian: 11, C: 67.1, H: 11.8, O: 4.2	31.5 NR	(<8: 54, 8 -8.9: 30, ≥9: 15)	6.6	45
	Metformin + sitagliptin, 464	54.4	55.8	AA: 6.7, Asian: 10.6, C: 63.1, H: 15.5	30.9 NR	(<8: 55, 8 -8.9: 31, ≥9: 14)	6	48
Wright, 2006[228]	Any in the sulfonylurea class, 1687	NR	NR	NR	NR NR	NR	NR	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin, 336	NR	NR	NR	NR NR	NR	NR	NR
	Total, 5063	52.4	59	AA: 8, Asian: 9, C: 83	27.5 NR	6.9	NR	NR
Rosenstock, 2006[140]	Metformin, 154	51.5	56	AA: 5, Asian: 14, C: 58, H: 21, O: <1	32.5 NR	8.8	2.9	31
	Metformin + rosiglitazone, 155	50.1	57	AA: 6, Asian: 12, C: 54, H: 26	33.2 NR	8.9	2.3	19
	Rosiglitazone, 159	50.6	58	AA: 5, Asian: 14, C: 59, H: 19, O: 3	32.8 NR	8.8	2.7	22
Jain, 2006[92]	Glyburide, 251	52.1	56.2	AA: 13.5, Asian: 0, C: 65.7, H: 19.9, Native American: 0.4, O: 0.4	32.8 94.3kg	9.2	0.78	123
	Pioglitazone, 251	52.1	53	AA: 15.9, Asian: 1.6, C: 61, H: 20.7, O: 0.4, Native American: 0.4	32.5 93.9kg	9.2	0.8	117
Stewart, 2006[160]	Metformin, 272	59	56	AA: <1, Asian: <1, C: 99, H: <1, Native Hawaiian/other Pacific Islander: <1	30.6 87.2 kg	7.2	3.7	54
	Metformin + rosiglitazone, 254	58.8	55	AA: 0, Asian: 1, C: 98, H: <1, Native Hawaiian /other pacific islander: 0	30.9 88.1 kg	7.2	3.7	50
Bakris, 2006[12]	Metformin + glyburide, 185	58.8	69	C: 76	31.8 90.3 kg	8.3	7.6	5
	Metformin + rosiglitazone, 204	60	63	C: 78	31.6 89.2 kg	8.5	8	10
Umpierrez, 2006[170]	Metformin + glimepiride, 96	51.6	55.2	AA: 13.5, Asian: 1.0, C: 79.2, H: 5.2, O: 1.0	34.54 NR	8.4	4.9	11
	Metformin + pioglitazone, 109	55.7	52.3	AA: 15.9, Asian: 3.7, C: 78.5, H: 1.9, O: 0	33.81 NR	8.31	5.9	17
Kvapil, 2006[105]	Metformin + aspart 70/30, 116	56.4	46	NR	30.4 85.1 kg	9.3	6.7	11
	Metformin + glibenclamide, 114	58.1	46	NR	30. 84.0 kg	9.4	8.1	5

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Karter, 2005[221]	Any in the sulfonylurea class, 5921	59.9	54.8	NR	NR NR	8.9	NR	0
	Metformin, 11937	59.9	52.5	NR	NR NR	9.6	NR	0
	Pioglitazone, 3556	60.2	51.1	NR	NR NR	9.6	NR	0
Agarwal, 2005[189]	Glipizide, 22	64	100	AA: 27, C: 73	34 102 kg	7.7	14	3
	Pioglitazone, 22	67	100	AA: 14, C: 86	32 97 kg	7.7	16	1
Derosa, 2005[36]	Metformin + glimepiride, 49	52	47	NR	26.8 NR	7.9	4	2
	Metformin + rosiglitazone, 50	54	50	NR	26.6 NR	8.0	5	2
Malone, 2004[204]	Metformin + glargine,	NR	NR	NR	NR NR	NR	NR	7
	Metformin + lispro 75/25,	NR	NR	NR	NR NR	NR	NR	3
	Pooled arms	NR	63	NR	30.9 91.5kg	8.7	9	NR
Malone, 2005[205]	Metformin + lispro 75/25, 50	59.18	50	NR	29.41 77.82 kg	8.5	13.52	3
	Metformin + glargine, 47	59.63	38	NR	29.64 77.21 kg	8.48	11.9	10
Madsbad, 2004[110]	Glimepiride, 27	57	59	NR	30.2 NR	7.8	3.8	0
	Liraglutide, 26	53	85	NR	30.2 NR	7.4	4.1	3
	Liraglutide, 25	58	60	NR	32 NR	7.9	4.4	3
	Liraglutide, 27	57	67	NR	30.1 NR	7.7	4.5	7
	Liraglutide, 30	57	67	NR	30.4 NR	7.4	4.6	2

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Liraglutide, 29	58	55	NR	31.9 NR	7.4	6.1	2
Malone, 2003[112]	Metformin + glibenclamide, 301	59	49	AA: 1, C: 89, H: 6, O: 4	29.6 81.7 kg	9.27	7.4	29
	Metformin + lispro 75/25, 296	58	57	AA: 0.7, C: 88.9, H: 7.4, O: 3	29.8 83.0 kg	9.17	8.0	25
Jones, 2003[202]	Metformin, 121	58 (38 to 78)	70	NR	34 NR	8.7	5	0
	Metformin, 22	64 (46 to 81)	9	NR	23 NR	8.6	6.5	NR
	Metformin, 82	60 (40 to 81)	74	NR	28 NR	8.8	6	NR
	Metformin + rosiglitazone, 141	58 (36 to 82)	69	NR	28 NR	8.8	6	NR
	Metformin + rosiglitazone, 142	57 (39 to 80)	57	NR	34 NR	8.8	5	NR
	Metformin + rosiglitazone, 35	62 (42 to 78)	71	NR	23 NR	9.3	8	NR
Leiter, 2005[108]	Metformin, 78	60	56	C: 86, Others: 22	32.2 NR	7.5	5.7	13
	Metformin + rosiglitazone, 158	58	65	C: 76, Others: 24	33 NR	7.5	5.3	18
Garber, 2006[65]	Diet + metformin + glibenclamide, 160	56 (31-78)	56	AA: 5, C: 80, Asian: 3, H: 11, O: 2	32 93 kg	8.5	5	NR
	Diet + metformin + rosiglitazone, 158	56 (24-78)	65	AA: 6, C: 79, Asian: 3, H: 10, O: 3	32 94 kg	8.4	6	NR
Weissman, 2005[174]	Metformin, 384	55.7	NR	NR	33.8 96.7kg	7.97	NR	95
	Metformin + rosiglitazone, 382	55.5	NR	NR	34.4 98.2kg	8.05	NR	76
	Metformin + rosiglitazone, 358	55.5	NR	NR	34.4 98.2kg	8.05	NR	95

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin, 351	55.7	NR	NR	33.8 96.7kg	7.97	NR	76
Bailey, 2005[9]	Metformin, 280	57.6	57	AA: <1, Asian: 1, C: 98, O: 1	32.1 89.5kg	7.5	6.1	44
	Metformin + rosiglitazone, 289	58.1	58	AA: 1, C: 97, Asian: 1, H: 0, O: 1	32.2 90.9kg	7.4	6	30
	Metformin + rosiglitazone, 288	58.1	58	AA: 1, Asian: 1, C: 97, O: 1	32.2 90.9kg	7.4	6	30
Yamanouchi, 2005[179]	Diet + exercise + glimepiride, 37	55.6 (46.3 - 64.9)	51	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.6 NR	9.8	3.3 months	3
	Diet + exercise + metformin, 39	54.7 (44.9 - 64.5)	51	AA: 0, C: 0, Asian: 0, H: 0, O: 100	26.2 NR	9.9	3 months	2
	Diet + exercise + pioglitazone, 38	55.2 (46 - 64.4)	47	AA: 0, C: 0, Asian: 0, H: 0, O: 100	25.8 NR	10.2	3.2 months	2
	Glimepiride, 37	55.6	51	NR	25.6 NR	9.8	3.3	3
	Metformin, 39	54.7	51	NR	26.2 NR	9.9	3	2
	Pioglitazone, 38	55.2	47	NR	25.8 NR	10.2	3.2	3
Derosa, 2005[37]	Diet + exercise + behavioral therapy + metformin + glimepiride, 47	52 (47 -57)	49	NR	26.8 NR	7.9	4	NR
	Diet + exercise + behavioral therapy + metformin + rosiglitazone, 48	54 (50 -58)	52	NR	26.6 NR	8	5	NR
Rajagopalan, 2005[225]	metformin, 1137	52.5 (19-88)	49.6	NR	NR NR	NR	NR	NR
	Pioglitazone, 1847	54.3 (18-91)	52.4	NR	NR NR	NR	NR	NR
	Unspecified sulfonylurea, 1474	54.5 (19-94)	52.9	NR	NR NR	NR	NR	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Pioglitazone, 1137	52.7 (18-90)	50	NR	NR NR	NR	NR	NR
	Pioglitazone, 1474	54.6 (18-91)	54.3	NR	NR NR	NR	NR	NR
	Rosiglitazone, 1847	54.3 (18-92)	51.8	NR	NR NR	NR	NR	NR
Feinglos, 2005[52]	Metformin + glipizide, 61	57.7 (30-80)	46	AA: 8.2, C: 78.7, Asian: 3.3, H: 8.2, O: 1.6	31.7 90 kg	7.45	6.5	NR
	Placebo + metformin, 61	58.8 (40-81)	41	AA: 16.4, C: 68.9, Asian: 3.3, H: 8.2, O: 3.3	32.1 90.8 kg	7.64	4.6	NR
Schernthaner, 2004[149]	Metformin, 597	56 (35 to 75)	58	NR	31.4 89.7kg	8.7	3.1	96
	Pioglitazone, 597	57 (35 to 75)	53	NR	31.2 88.2kg	8.7	3.4	98
	Placebo + diet + metformin, 597	56	57.8	NR	31.4 89.7kg	8.7	3.1	NR
	Placebo + diet + pioglitazone, 597	57	52.6	NR	31.2 88.2kg	8.7	3.4	NR
Derosa, 2004[34]	Placebo + diet + exercise + glimepiride, 81	56	47	NR	27.6 NR	8.5	NR	NR
	Placebo + diet + exercise + metformin, 83	58	51	NR	28.1 NR	8.4	NR	NR
Tan, 2004[162]	Glibenclamide, 109	57.9	73	AA: 0, C: 100, Asian: 0, H: 0, O: 0	29.6 89 kg	8.5	5.22	41
	Pioglitazone, 91	60	62	C: 99, Unspecified: 1	30.2 88.4 kg	8.4	4.76	36
Hanefeld, 2004[81]	Metformin + sulfonylurea, 320	60 (36 to 75)	54.7	AA: 0.9, C: 98.4, O: 0.6	30 84.9 kg	8.8	7.1	279
	Pioglitazone + sulfonylurea, 319	60 (36 to 75)	53,6	AA: 0.6, C: 99.4, O: 0	30.2 85.3 kg	8.82	60	259
	Placebo + metformin + unspecified sulfonylurea, 320	60 (36 to 75)	54.7	AA: 0.9, C: 98.4, Asian: 0, H: 0, O: 0.6	30 84.9 kg	8.8	7.1	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Placebo + unspecified sulfonylurea + pioglitazone, 31	60 (36 to 75)	53.6	AA: 0.6, C: 99.4, Asian: 0, H: 0, O: 0	30.2 85.3 kg	8.82	7	NR
Garber, 2003[64]	Metformin + glyburide, 171	55.6	44	AA: 10.5, C: 77.2, Asian: 0, H: 8.8, O: 3.5	31.4 91.9 kg	8.8	3	NR
	Metformin, 164	54.7	43.3	AA: 6.7, C: 80.5, Asian: 0, H: 9.1, O: 3.7	31.4 92.8 kg	8.5	2.6	NR
	Glyburide, 151	55.3	43.7	AA: 7.3, C: 81.5, Asian: 0, H: 7.9, O: 3.3	31.1 91 kg	8.7	3	NR
Tosi, 2003[167]	Glibenclamide, 20	NR	NR	NR	NR NR	NR	NR	NR
	Metformin + glibenclamide, 41	NR	NR	NR	NR NR	NR	NR	NR
	Metformin, 19	NR	NR	NR	NR NR	NR	NR	NR
Goldstein, 2003[71]	Metformin + glipizide, 87	54.6	58.6	AA: 11.5, C: 72.4, Asian: 0, H: 16.1, O: 0	31.7 94 kg	8.7	5.9	NR
	Glipizide, 84	57.4	64.3	AA: 11.9, C: 71.4, Asian: 2.4, H: 14.3, O: 0	30.6 89.9 kg	8.9	6.5	NR
	Metformin, 76	56.6	61.8	AA: 15.8, C: 65.8, Asian: 1.3, H: 17.1, O: 0	31.6 93.8 kg	8.7	7.3	NR
Pavo, 2003[123]	Metformin, 100	55.8	56	NR	31.1 88.9 kg	8.6	6.3	9
	Pioglitazone, 105	54.2	56.2	NR	31.3 86.6 kg	8.6	5.6	5
Blonde, 2002[16]	Metformin + glyburide, 162	55.6	63.6	AA: 9.3, C: 67.9, Asian: 0, H: 19.1, O: 3.7	30.6 89.6 kg	9.42	6.97	NR
	Glyburide, 164	55.8	57.3	AA: 12.2, C: 66.5, Asian: 0, H: 17.1, O: 4.3	30.3 88 kg	9.64	7.01	NR
	Metformin + glyburide, 160	55.4	55.6	AA: 12.5, C: 70, Asian: 0, H: 15.6, O: 1.9	30.7 89.4 kg	9.41	7.36	NR
	Metformin, 153	57.6	62.1	AA: 10.5, C: 69.3, Asian: 0, H: 17, O: 3.3	30.6 89.5 kg	9.51	8.18	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
St John Sutton, 2002[159]	Glyburide, 99	56.1	72	AA: 3, C: 76, others: 21	NR 85.1 kg	9.5	6.2	NR
	Rosiglitazone, 104	55.1	72	AA: 5, C: 73, others: 22	NR 82.6 kg	9.1	5.3	NR
Marre, 2002[113]	Glibenclamide, 103	58.7	55	NR	29.3 82.5 kg	7.88	6.6	NR
	Metformin, 104	57.5	60	NR	29.9 84.9 kg	8.09	5.4	NR
	Metformin + glibenclamide, 101	58	50	NR	30.1 84.7 kg	7.89	5.9	NR
	Metformin + glibenclamide, 103	60.7	54	NR	29.7 83.1 kg	7.62	6.7	NR
Garber, 2002[63]	Metformin + glyburide, 165	58.1	58	AA: 6, C: 79, Asian: 0, H: 10, O: 5	29.6 86.7 kg	8.18	3.3	NR
	Glyburide, 161	56.5	51	AA: 9, C: 78, Asian: 0, H: 9, O: 4	30.3 87.2 kg	8.21	2.81	NR
	Metformin + glyburide, 158	56.9	58	AA: 13, C: 74, Asian: 0, H: 11, O: 2	30.1 88.8 kg	8.25	3.52	NR
	Metformin, 161	56	58	AA: 4, C: 81, Asian: 0, H: 12, O: 2	30.4 88.6 kg	8.26	2.98	NR
Gomez-Perez, 2002[73]	Metformin, 34	53.4 (40 - 68)	29.4	C: 2.9, H: 76.5, Mestizo: 20.6	28.5 NR	NR	9.1	NR
	Metformin + rosiglitazone, 35	51.7 (40 - 73)	28.6	C: 0, H: 80, Mestizo: 20	28.0 NR	NR	11.1	NR
	Metformin + rosiglitazone, 36	54.2 (42-76)	40	C: 11.1, H: 72.2, Mestizo: 16.7	27.6 NR	NR	10.7	NR
Charpentier, 2001[22]	Metformin + glimepiride, 147	56.8 (36-70)	59	NR	29.5 81.2 kg	6.4	5.6	NR
	Placebo + glimepiride, 150	55.4 (35-70)	58	NR	29.3 81 kg	6.5	5.3	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Placebo + metformin, 75	56.7 (36-69)	60	NR	29.2 82.2 kg	6.8	7	NR
Amador-Licona, 2000[186]	Metformin, 28	49.3	39	NR	26.8 70.7 kg	8.5	4.5	NR
	Glibenclamide, 23	48.2	30	NR	30.4 73.2 kg	8.4	4	NR
Einhorn, 2000[45]	Diet + metformin + pioglitazone, 168	55.5	54.8	AA: 8.3, C: 81, Asian: 0, H: 10.1, O: 0.6	32.11 NR	9.86	NR	NR
	Metformin, 160	55.7	60	AA: 6.3, C: 86.9, H: 3.8, Others: 3.1	32.12 NR	9.75	NR	37
	Metformin + pioglitazone, 168	55.5	54.8	AA: 8.3, C: 81, H: 10.1, Others: 0.6	32.11 NR	9.86	NR	21
	Placebo + diet + metformin, 160	55.7	60	AA: 6.3, C: 86.9, Asian: 0, H: 3.8, O: 3.1	32.12 NR	9.75	NR	NR
Fonseca, 2000[55]	Metformin, 116	58.8	74.3	AA: 3.5, C: 81.4, O: 15	30.3 NR	8.6	7.3	22
	Metformin + rosiglitazone, 113	58.3	68.2	AA: 10, C: 77.3, others: 12.7	29.8 NR	8.9	8.3	18
	Metformin + rosiglitazone, 119	57.5	62.1	AA: 6.9, C: 80.2, others: 12.9	30.2 NR	8.9	7.5	18
DeFronzo, 1995[27]	Metformin, 143	53	43	NR	29.9 94.4 kg	8.4	6	NR
	Metformin + glyburide, 213	55	46	NR	29 92.1 kg	8.8	7.8	NR
	Placebo + glyburide, 209	56	49	NR	29.1 92.6 kg	8.5	8.7	NR
	Placebo + metformin, 210	55	46	NR	29.4 92.6 kg	8.9	8.4	NR
Hermann, 1994[86]	Diet + metformin + glibenclamide, 54	NR	NR	NR	NR 80.2 kg	6.8	NR	NR
	Diet + metformin, 25	NR	NR	NR	NR 78.6 kg	6.9	NR	NR

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Diet + metformin + glibenclamide, 13	NR	NR	NR	NR 84.6 kg	7.8	NR	NR
	Diet + metformin + glibenclamide, 13	NR	NR	NR	NR 76 kg	7.8	NR	NR
	Diet + metformin + glibenclamide, 18	NR	NR	NR	NR 83.2 kg	8.4	NR	NR
	Diet + glibenclamide, 21	NR	NR	NR	NR 82.6 kg	6.7	NR	NR
Ahren, 2014[2]	Metformin + placebo 104	56.1	49.5	C: 63.4, AA: 22.8, Asian: 5, H: 31.7	32.8 91.6 kg	8.2	6.7	42
	Metformin + glimepiride + placebo 317	54.4	51.5	C: 71.7, AA: 12.7, Asian: 5.2, H: 34.9	32.5 91.8 kg	8.1	6	99
	Metformin + sitagliptin + placebo 313	54.3	46	C: 74.5, AA: 11.6, Asian: 6.6, H: 36.8	32.5 90.3 kg	8.1	5.8	101
	Metformin + albiglutide + placebo 315	54.3	44.7	C: 70.9, AA: 17.5, Asian: 6, H: 32.8	32.7 89.6 kg	8.1	6	100
Alba, 2013[3]	Pioglitazone 54	53.4	42.6	C: 79.6, AA: 16.7, Asian: 1.9, H: 38.9, O: 1.9	86.6kg	7.9	2.4	2
	Sitagliptin 52	54.6	53.8	C: 86.5, AA: 11.5, Asian: 1.9, H: 36.4, O: 0	85.7kg	7.7	2.4	6
Andersson, 2010[190]	Metformin 688	69	62		NR			
	Sulfonylurea	76	57		NR			
	Metformin + Sulfonylurea	71	56		NR			
Arechavaleta, 2011[5]	Metformin + glimepiride + placebo, 519	56.2	53.8	C: 57.4, AA: 1.2, Asian: 21.4, O: 20	82		6.7	51
	Metformin + sitagliptin + placebo, 516	56.3	55	C: 57.6, AA: 1.2, Asian: 21.1, O: 20.1	80.6		6.8	48

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Arjona Ferreira, 2013[6]	Glipizide + placebo 212	64.3	54.9	C: 28.2, AA: 1.4, Asian: 58.5, H: 28.9, O: 12	70.2kg	7.8	10.1	
	Sitagliptin + placebo 211	64.8	59.3	C: 29.6, AA: 1.5, Asian: 53.3, H: 33.3, O: 15.5	68.0kg	7.8	10.7	
Aschner, 2012[8]	Metformin + sitagliptin 265	53.3	52		84.2	8.5	4.8	12
	Metformin + insulin glargine 250	53.9	50		83.4	8.5	3.9	23
Bailey, 2013[10]	Metformin + placebo 137	53.7	55		31.8	8.11	5.8	64
	Metformin + dapagliflozin + placebo, 137	55	51		31.6	7.99	6	55
	Metformin + dapagliflozin 137	54.3	50		31.4	8.17	6.4	48
	Metformin + dapagliflozin + placebo, 135	52.7	57		31.2	7.92	6.1	40
Barnett, 2012[13]	Glimepiride 76	56.7	43.4	C: 67.1, Asian: 27.6, O: 5.3	80.9 kg	8.1		18
	Linagliptin 151	56.4	36.4	C: 70.2, Asian: 27.8, O: 2	77.0 kg	8.1		32
Bergenstal, 2010[14]	Metformin + pioglitazone + placebo 165	53	48	C: 39, AA: 8, Asian: 24, H: 27, O: 2	88 kg	8.5	6	
	Metformin + sitagliptin + placebo 166	52	52	C: 30, AA: 12, Asian: 25, H: 30, O: 3	87 kg	8.5	5	
	Metformin + exenatide + placebo 160	52	56	C: 33, AA: 12, Asian: 23, H: 31, O: 1	32 89 kg	8.6	6	
Bergenstal, 2012[15]	Metformin + placebo 93	56.1	52	C: 77, AA: 6, Asian: 10, H: 11, O: 8	91.1 kg	8.03	5.5	10
	Metformin + sitagliptin + placebo, 185	55.5	59	C: 76, AA: 6, Asian: 11, H: 16, O: 7	92.5 kg	7.94	6	13

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
Bolinder, 2012[17]	Metformin + placebo 91	60.8	56	C: 100, AA: 0, Asian: 0, H: 0, O: 0	31.7 90.9 kg	7.16	5.5	20
	Metformin + dapagliflozin 91	60.6	55.1	C: 100, AA: 0, Asian: 0, H: 0, O: 0	32.1 92.1 kg	7.19	6	20
Borges, 2011[18]	Metformin 340	50.7	53	C: 55, AA: 4, Asian: 34, O: 6	90.6 kg	8.6	2.6	154
	Metformin + rosiglitazone 348	51.5	53	C: 53, AA: 5, Asian: 35, O: 6	87.1 kg	8.6	2.3	131
Cefalu, 2013[20]	Metformin + glimepiride 484	56.3	55	C: 67, AA: 5, Asian: 19, O: 9	86.5 kg	7.8	6.6	98
	Metformin + canagliflozin 483	56.4	52	C: 67, AA: 4, Asian: 21, O: 9	86.9 kg	7.8	6.5	88
	Metformin + canagliflozin 485	55.8	50	C: 69, AA: 4, Asian: 19, O: 9	86.6 kg	7.8	6.7	105
Chawla, 2013[23]	Metformin + pioglitazone 25	52.2	56		72.68kg		4.458	0
	Metformin + sitagliptin 27	49.48	56		72.1		4.107	2
Curkendall, 2014[216]	Metformin + Sulfonylurea	56.5	55.9		NR			
	Metformin + saxagliptin	55.4	53.2		NR			
Davies, 2013[218]	Metformin + exenatide 111	59	64	C: 94, AA: 1, Asian: 5	96.7kg	8.37	8	
	Metformin + insulin detemir 105	58	69	C: 97, AA: 0, Asian: 3	97.9kg	8.35	7	
DeFronzo, 2012[31]	Metformin + placebo 129	55.2	47.3	C: 72.1, AA: 6.2, Asian: 3.9, H: 48.8, O: 17.8	30.6	8.5	6	
	Metformin + pioglitazone + placebo, 130	54.1	46.9	C: 65.4, AA: 6.2, Asian: 8.5, H: 48.5, O: 20	31.3	8.5	5.7	
	Metformin + pioglitazone + placebo, 129	56.1	48.8	C: 74.4, AA: 4.7, Asian: 7.8, H: 51.9, O: 13.2	31.4	8.5	7.6	

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + pioglitazone + placebo, 129	54.5	41.1	C: 65.9, AA: 7, Asian: 9.3, H: 47.3, O: 17.8	30.7	8.5	5.7	
	Metformin + alogliptin + placebo, 128	53.1	52.3	C: 69.5, AA: 4.7, Asian: 10.9, H: 46.9, O: 14.8	31	8.6	6.2	
	Metformin + alogliptin + placebo, 129	53.7	38.8	C: 62, AA: 3.9, Asian: 11.6, H: 48.8, O: 22.5	31.5	8.6	5.6	
Derosa, 2013[42]	Metformin + placebo 87	54.8	51		78.6kg	8	5.4	5
	Metformin + sitagliptin 91	55.9	46		78.4kg	8.1	5.8	7
Derosa, 2013[43]	Metformin + placebo 85	56.7	48	C: 100	90.5kg	7.9	7.8	5
	Metformin + exenatide 86	57.3	50	C: 100	89.0kg	8.1	7.6	5
Diamant, 2010[44]	Metformin + exenatide 164				NR			
	Metformin + insulin glargine 157				NR			
Erem, 2014[47]	Metformin 20	52.2	30		87.47kg	7.62		1
	Pioglitazone 20	52.5	25		81.93kg	8.03		1
Esposito, 2011[48] }	Metformin 55	54.9	50.9		83.5kg	8.1		4
	Pioglitazone 55	54.2	54.5		84.5kg	8		4
Farcasiu, 2011[51]	Metformin + insulin lispro 75/25 151	58.4	45.7	C: 98.7, AA: 1.3, O: 1.3	85.1 kg	8.5	11.5	23
	Metformin + insulin lispro 50/50 151	57	39.1	C: 99.3, AA: 0.7	32.3 88.6 kg	8.6	10.9	23
Ferrannini,	Metformin 56	58	50	C: 69.6, AA: 1.8, Asian: 25	85.8kg	8.15		

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
2013[53]	Empagliflozin 106	59	46.2	C: 79.2, AA: 0, Asian: 19.8	82.9kg	7.89		
	Empagliflozin 109	59	52.3	C: 77.1		8		
	Metformin + sitagliptin 56	60	51.8	C: 100		8.03		
	Metformin + empagliflozin 166	60	50	C: 98.2		7.88		
	Metformin + empagliflozin 166	60	53	C: 98.8		7.91		
Ferrannini, 2013[194]	Metformin		48.8	C: 60				
	Empagliflozin		49.4	C: 64.2				
	Empagliflozin		50	C: 65.9				
Fonseca, 2012[56]	Metformin 144	55.5	51	C: 13		8.4	5.9	25
	Metformin + saxagliptin 138	55.2	41	C: 9		8.3	6.5	8
Forst, 2010[57]	Metformin + placebo 71	60.1	62	C: 97		8.4	6.2	14
	Metformin + glimepiride 65	59.4	63.1	C: 99		8.2	6.7	4
	Metformin + linagliptin 66	59.6	56.1	C: 100		8.5	7.3	10
Forst, 2014[59]	Metformin + glimepiride 20	63	70			7.4	8	0
	Metformin + linagliptin 20	65	65			7.3	7.7	1
Gallwitz, 2011[60]	Metformin + exenatide 182	57					5	47
	Metformin + insulin aspart 70/30, 181	57					5	44
Gallwitz,	Metformin + glimepiride +	59.8	61	C: 85		7.7		

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
2012[61]	placebo, 775							
	Metformin + linagliptin + placebo, 777	59.8	60	C: 85		7.7		
Gallwitz, 2012[62]	Metformin + glimepiride 514	56	52	C: 91		7.4	5.5	128
	Metformin + exenatide 515	56	56	C: 92		7.5	5.8	174
Garber, 2011[67]	Glimepiride + placebo 248	53.4	54	C: 77		8.2	5.6	151
	Liraglutide + placebo 251	53.7	47	C: 80		8.2	5.2	141
	Liraglutide + placebo 247	52	49	C: 75		8.2	5.3	132
Genovese, 2013[68]	Metformin + placebo 103	57.8	60.2	C: 100		7.02	5.7	6
	Metformin + pioglitazone 110	57	59.1	C: 100		6.92	5.8	13
Genovese, 2013[69]	Metformin 29	56.4	65.5			6.8	3.9	3
	Pioglitazone + placebo 29	59.1	48.3			6.9	4.4	5
Goke, 2010[70]	Metformin + glipizide 430	57.6	54	C: 84.2		7.7	5.4	283
	Metformin + saxagliptin 428	57.5	49.5	C: 82.2		7.7	5.5	263
Gupta, 2013[76]	Glimepiride 83	40.07				8.02		12
	Sitagliptin 84	39.12				8.03		7
Haak, 2012[77]	Metformin 144	52.9	56.9	C: 64.6, AA: 0, Asian: 35.4, O: 0	79.9	8.7		17
	Metformin 147	55.2	53.1	C: 64.6, AA: 1.4, Asian: 34, O: 0	80	8.5		21
	Linagliptin 142	56.2	56.3	C: 68.3, AA: 0, Asian: 31.7, O: 0	79.1	8.7		21

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + linagliptin 143	55.6	51	C: 72, AA: 1.4, Asian: 25.9, O: 0.7	80.8	8.7		16
	Metformin + linagliptin 143	56.4	53.8	C: 65.7, AA: 0.7, Asian: 33.6, O: 0	76.7	8.7		11
Haak, 2013[78]	Metformin 170	55.7	55.7	C: 63.9, AA: 0, Asian: 36.1	Median92.6 kg 29.5	7.76		
	Metformin + linagliptin 170	55.6	54.1	C: 62.4, AA: 0.9, Asian: 36.7	Median89 kg 29.2	7.31		
	Metformin + linagliptin 225	55.1	55.4	C: 65.2, AA: 0, Asian: 34.8	Median88.8kg 28.3	7.95		
Haring, 2014[83]	Metformin + placebo 225	56.8	51.3	C: 71.7, AA: 1.8, Asian: 26.5	Median87.8kg 29.8	7.34		
	Metformin + empagliflozin 171	56.1	61.7	C: 68.3, AA: 0, Asian: 31.7	Median84.1kg 28.8	8.15		
	Metformin + empagliflozin 171	55.6	54.1	C: 60.4, AA: 0.9, Asian: 38.7	Median88.6 kg 28.5	6.93		
Henry, 2012[84]	Metformin + placebo 207	56	56	C: 55, AA: 1, Asian: 44, O: 0	79.7kg	7.9		21
	Dapagliflozin + placebo 217	55.5	58	C: 52, AA: 2, Asian: 46, O: 1	81.6kg	7.94		8
	Metformin + dapagliflozin 214	55.6	56	C: 53, AA: 0, Asian: 46, O: 1	82.2kg	7.86		18
Henry, 2012[84]	Metformin + placebo	51.8	24		85.6kg	9.2	0.6	30
	Dapagliflozin + placebo	52.3	22		86.2kg	9.1	0.4	33
	Metformin + dapagliflozin	51.7	21		84.1kg	9.2	0.3	17
Hermans,	Metformin	52.7	46.6		87.2	9.1	0.5	27

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
2012[87]								
	Metformin + saxagliptin	51.1	47.9		88.5	9.1	0.6	31
Hong, 2013[195]	Metformin + placebo	51	50.2		88.4	9.1	0.6	28
	Glipizide + placebo 139	58.6	54.7	C: 97.1, AA: 0.7, Asian: 1.4, O: 0.7	31.2		6.9	32
Ji, 2015[93]	Metformin, 345	52.9	45.8	C: 22.6, AA: 0.9, Asian: 47.8, O: 28.7	29 NR	8	NR	14
	Metformin + linagliptin, 344	53.1	49.1	C: 27.9, AA: 0, Asian: 47.4, O: 24.7	29 NR	8	NR	14
Kadoglou, 2011[95]	Metformin 147	58.7	59.9	C: 98.6, AA: 0.7, Asian: 0.7, O: 0	32.1		6	28
	Metformin + rosiglitazone 156	62.8	78.2		69.6kg	7.6	5.6	32
Kadowaki, 2013[96]	Metformin + placebo 148	63.8	77		68.7kg	7.6	5.6	31
	Metformin + sitagliptin 70	62.7	27		30.04	7.56	2.7	
Kaku, 2011[99]	Glibenclamide 70	62	26		29.68	7.58	1.8	
	Liraglutide 72	57.2	68.1		25	8.4	7.3	
Kikuchi, 2012[101]	Rosiglitazone 77	59.6	71.4		25.2	8.2	7.7	
	Pioglitazone	58.5	65.2	Asian: 100	65.4 kg	9.18	8.5	
Kim, 2014[103]	Metformin	58.2	68.3	Asian: 100	66.2 kg	9.32	8.1	
	Metformin + glimepiride 160	55	62.9	Asian: 100	24.5	8.9	5	11
Lavalle-Gonzalez, 2013[106]	Metformin + placebo 159	56	62.3	Asian: 100	24.9	8.8	4.2	22
	Metformin + sitagliptin	56.1	47.2		25.7	7.8		14

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	108				66.9 kg			
	Metformin + canagliflozin 101	55.2	51.5		25.5 66.5 kg	7.9		6
Lavalle-Gonzalez, 2013[106]	Metformin + canagliflozin 183	55.3	51.4	C: 70.5, AA: 1.6, Asian: 16.4, O: 11.5	86.6kg	8	6.8	28
Lee, 2013[223]	Metformin + pioglitazone 366	55.5	47	C: 72.1, AA: 3.6, Asian: 11.2, O: 13.1	87.7kg	7.9	6.8	47
Lee, 2013[223]	Metformin + sitagliptin 368	55.5	47.3	C: 68.5, AA: 4.3, Asian: 13.9, O: 13.3	88.8kg	7.9	6.7	46
Lee, 2013[223]	Albiglutide + Sulfonylurea 367	55.3	45	C: 69.8, AA: 3.5, Asian: 16.3, O: 10.4	85.4kg	7.9	7.1	44
Lehman, 2012[224]	Metformin	55.2	60	Asian: 100	26.3 71.4 kg	8.8	5	3
	Sulfonylurea	50.2	63.2	Asian: 100	74.5 27.3	9.4	1	5
List, 2009[109]	Metformin	54.8	51.6	Asian: 100	26.5 69.9kg	8.9	1	3
	Dapagliflozin 175	67.81	100	C: 84, AA: 7.43, H: 8.57, O: 0	29.67	6.52		
	Dapagliflozin 533	64.7	100	C: 82.36, AA: 9.94, H: 7.32, O: 0.38	30.97	6.48		
Maffioli, 2013[111]	Metformin + pioglitazone 1930	72.33	100	C: 79.74, AA: 13.32, H: 6.42, O: 0.52	28.91	6.77		
	Metformin + glibenclamide 2404	69.87	100	C: 82.12, AA: 10.94, H: 6.61, O: 0.33	29.86	6.79		
Moon, 2014[114]	Metformin + glimepiride 56	54	48		88 kg	7.6		5
	Metformin + insulin glargine 58	55	48		89 kg	8		3
Nauck, 2009[119]	Metformin + placebo 47	54	53		86 kg	8		7
Nauck, 2009[119]	Metformin + alogliptin 86	62.8	48		83.5	8.4		3
	Metformin + alogliptin	61.4	50		83.1	8.2		2

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	84							
Nauck, 2011[120]	Metformin + glipizide 36	54.9	47.1		66.0 kg	8.9	95.6	2
	Metformin + dapagliflozin 39	51.3	31.6		62.7 kg	8.8	79	0
Nauck, 2014[121]	Metformin + placebo 104	56	48	C: 76, AA: 7, Asian: 6, H: 24, O: 11	32	8	6	
	Metformin + sitagliptin 210	54	54.3	C: 76, AA: 6, Asian: 9, H: 32, O: 9	32	7.9	6	
	Metformin + dulaglutide 213	55	47.4	C: 80, AA: 2, Asian: 8, H: 31, O: 10	32	7.9	6	
	Metformin + dulaglutide 408	59	54.9	C: 80.5, AA: 6, Asian: 8.5, O: 5	31.2	7.7	7	94
Perez-Monteverde, 2011[124]	Pioglitazone 406	58	55.3	C: 81.8, AA: 6.5, Asian: 6.8, O: 5	31.7	7.7	6	84
	Sitagliptin 177	55	51	C: 51, AA: 5, Asian: 22, H: 22, O: 0	87 kg	8.1	7	
Pfutzner, 2011[128] }	Metformin + pioglitazone 315	54	48	C: 50, AA: 2, Asian: 26, H: 21, O: 1	86 kg	8.1	7	
	Metformin + glimepiride 302	54	44	C: 54, AA: 4, Asian: 26, H: 17, O: 0	86 kg	8.2	7	
Pfutzner, 2011[129]	Metformin + placebo 304	54	48	C: 52, AA: 5, Asian: 25, H: 18, O: 0	87 kg	8.1	7	
	Saxagliptin + placebo 248	51.7	59.7	C: 55.2, AA: 4.4, Asian: 12.9, H: 45.2, O: 8.5	82.2 kg	9.1	3.5	17
	Metformin + saxagliptin 248	51.7	59.7	C: 55.2, AA: 4.4, Asian: 12.9, H: 45.2, O: 8.5	82.2 kg	9.1	3.5	17
	Metformin + saxagliptin	59	66		32.6		6.2	32
Pratley, 2014[131]	Metformin	59	64		32.5		5.9	29
	Metformin 328	51.8	49.7	C: 76.5, AA: 1.2, Asian: 15.9, O: 6.4	30.2	9.4	1.7	109
	Metformin + alogliptin 335	52.1	50.4	C: 76.1, AA: 1.8, Asian: 16.7, O: 5.4	30.2	9.6	1.7	126

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Metformin + alogliptin 320	52	51.6	C: 76.9, AA: 2.2, Asian: 15.9, O: 5	29.9	9.4	2	91
	+ alogliptin 323	52.1	45.2	C: 75.2, AA: 2.2, Asian: 16.7, O: 5.9	30.4	9.5	1.4	92
Qiu, 2014[132]	Metformin + placebo 114	54.6	41.2	C: 74.6, AA: 5.3, Asian: 16.7, O: 3.5	30.2	8.5	3.8	
	Metformin + canagliflozin 111	52.6	45.9	C: 71.2, AA: 5.4, Asian: 18, O: 5.4	30.5	8.39	4.1	
	Metformin + canagliflozin 111	53.7	43.2	C: 68.5, AA: 5.4, Asian: 18, O: 8.1	30.9	8.5	4.1	
Reasner, 2011[135]	Metformin 114	54.6	54.4	C: 68.4, AA: 4.4, Asian: 22.8, O: 4.4	31	8.43	4.2	
	Metformin + sitagliptin 112	52.6	42.9	C: 75, AA: 2.7, Asian: 15.2, O: 7.1	30.8	8.3	3.6	
Ridderstrale, 2014[136]	Metformin + glimepiride 93	57	49.5	C: 78.5, AA: 4.3, Asian: 9.7, O: 7.5	90.5kg	7.7	7	7
	Metformin + empagliflozin 93	58.6	43	C: 80.6, AA: 5.4, Asian: 3.2, O: 10.8	91.2kg	7.6	6.7	8
Roden, 2013[139]	Sitagliptin 93	56.7	47.3	C: 89.2, AA: 1.1, Asian: 6.5, O: 3.2	90.2kg	7.6	7.3	13
	Empagliflozin	50	57	C: 79, AA: 14, Asian: 4, H: 30, O: 3	33.7 97.2 kg	9.8	3.2	215
	Empagliflozin	49.4	56	C: 81, AA: 13, Asian: 3, H: 36, O: 3	32.9 94.7 kg	9.9	3.5	216
Rosenstock, 2010[141]	Pioglitazone + placebo 780	55.7	54	C: 67, AA: 1, Asian: 32, H: 20, O: 0	83.0kg	7.92		132
	Alogliptin + placebo 769	56.2	56	C: 65, AA: 2, Asian: 33, H: 20, O: <1	82.5kg	7.92		121
Rosenstock, 2012[142]	Metformin + placebo 223	55.1	63	C: 34, AA: 1, Asian: 64, O: <1	79.3kg	7.85		17
	Metformin + sitagliptin 224	56.2	63	C: 34, AA: 1, Asian: 64, O: 0	78.4kg	7.87		18
	Metformin + canagliflozin 224	53.8	65	C: 33, AA: 3, Asian: 64, O: 0	77.8kg	7.86		20
	Metformin + canagliflozin					8.76		37

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	163							
	Metformin + canagliflozin 164					8.8		38
Rosenstock, 2013[143]	Glipizide 65	53.3	48		85.9 kg	7.75	6.4	10
	Alogliptin 65	51.7	58		87.2 kg	7.64	5.6	5
Rosenstock, 2013[144]	Metformin + placebo 64	51.7	56		87.7 kg	7.83	6.1	5
	Metformin + sitagliptin 65	52.9	51		87.7 kg	7.61	6.4	9
	Metformin + empagliflozin 64	52.3	56		87.3 kg	7.69	5.9	8
	Metformin + empagliflozin 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02	7.45	5.94	
Ross, 2012[146]	Metformin + placebo 219	69.8	43.8	C: 70.3, AA: 9.1, Asian: 11.9, O: 8.6	30.02	7.45	5.94	
	Metformin + linagliptin + placebo 71	60	47	C: 90, AA: 1, H: 9, O: 0	87.7kg	8		5
Russell-Jones, 2012[147]	Metformin + placebo 71	58	54	C: 87, AA: 0, H: 13, O: 0	88.0kg	8.1		1
	Pioglitazone + placebo 71	59	47	C: 78, AA: 3, H: 20, O: 0	87.9kg	7.9		5
	Sitagliptin + placebo 70	59	53	C: 83, AA: 1, H: 16, O: 0	90.5kg	8.1		0
	Exenatide + placebo 44	59.9	47.7	C: 72.7, Asian: 27.3, O: 0	77.7kg	7.92		1
Schernthaner, 2015[148]	Metformin + glimepiride + placebo, 360	72.7	63.3	C: 98.6, O: 1.4	29.3 NR	7.62	NR	75
	Metformin + saxagliptin + placebo, 360	72.5	60.3	C: 97.8, : 2.2	29.9 NR	7.58	NR	71
Seino, 2012[156]	Metformin + placebo 224	58.4	54	C: 62.1, Asian: 36.6, O: 1.3	80.6kg	7.98		10
	Metformin + alogliptin	54	62.6	C: 65, AA: 4.5, Asian:	85.9 kg	8.6	2.6	

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	246			20.7, H: 8.5, O: 1.2				
	Metformin + alogliptin 163	55	59.5	C: 67.5, AA: 2.5, Asian: 20.9, H: 9.2, O: 0	86.1 kg	8.5	2.7	
Shihara, 2011[157]	Pioglitazone 163	52	57.7	C: 69.3, AA: 1.8, Asian: 20.2, H: 8, O: 0.6	88.7 kg	8.5	2.7	
	Sulfonylurea 248	54	56	C: 68.1, AA: 2.8, Asian: 22.2, H: 6.5, O: 0.4	87.5 kg	8.5	2.7	
Skrivanek, 2014[226]	Metformin + placebo 100	52.1	72		69.89 kg	8	6.04	0
	Metformin + sitagliptin 92	53.4	65.2		69.47 kg	7.89	6.34	1
	Metformin + dulaglutide 96	52.3	68.8		69.65 kg	8.02	6.62	3
	Metformin + dulaglutide 96	56.8	68	Asian: 100	65.5 kg	7.8	4.1	5
	Metformin + dulaglutide 95	57.7	65	Asian: 100	65.6 kg	7.8	6	9
Srivastava, 2012[158]	Metformin + glimepiride 38	53	32	C: 40, AA: 5, Asian: 11, H: 45, O: 0	32	8.1	7	4
	Metformin + sitagliptin 42	53	50	C: 48, AA: 5, Asian: 10, H: 38, O: 0	32	8.4	9	0
Stenlof, 2014[213]	Sitagliptin 21	52	48	C: 62, AA: 0, Asian: 5, H: 33, O: 0	33	8.2	7	0
	Canagliflozin 10	55	30	C: 40, AA: 0, Asian: 0, H: 60, O: 0	34	7.9	7	2
	Canagliflozin 25	53	40	C: 40, AA: 8, Asian: 8, H: 44, O: 0	32	8.7	9	1
Taskinen, 2011[164]	Metformin + placebo 25			Asian: 100	26.5			0
	Metformin + linagliptin 25			Asian: 100	25.3			0
Umpierrez, 2014[171]	Metformin + placebo 170	55.1	41.5	C: 63.6, AA: 9.2, Asian: 13.8, O: 13.3	85.8kg	8.1	4.5	18
	Dulaglutide + placebo 170	55.3	45.2	C: 69.5, AA: 7.1, Asian: 14.7, O: 8.6	86.9kg	8	4.3	5

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	Dulaglutide + placebo 155	55.7	45.8	C: 69.8, AA: 4.7, Asian: 15.1, O: 10.4	87.6kg	8	4.2	20
van Staa, 2012[230]	Metformin 177	56.6	57	C: 79, Asian: 18, O: 3	83.3 kg	8.02		14
	Thiazolidinedione 523	56.5	53	C: 75, Asian: 22, O: 3	82.2 kg	8.09		39
	Sulfonylurea 268	55	45	C: 75, AA: 5, Asian: 8, H: 35, O: 13	33 92 kg	7.6	3	55
Wang, 2015[173]	Metformin + placebo, 101	26.5	50	Asian: 100	25.8 NR	8	NR	12
	Metformin + linagliptin, 205	55.1	49.8	Asian:100	25.5 NR	7.99	NR	14
Weir, 2011[227]	Metformin 270	56	44	C: 73, AA: 8, Asian: 7, H: 32, O: 11	92 kg 33	7.6	3	52
	Glyburide 269	56	42	C: 75, AA: 6, Asian: 8, H: 33, O: 12	34 93 kg	7.6	3	49
	+ basal insulin 109,708	63	56.3		31	8.8		
White, 2014[175]	Metformin + placebo 31,372	63	57.3		31	8.9		
	Metformin + saxagliptin 68,029	65	56.1		30	9		
Williams-Herman, 2010[177]	Metformin + placebo 572		51.4		NR			
	Metformin + placebo 580		46.7		NR			0
	Metformin + placebo 193		50.8		NR			
	Sitagliptin + placebo 444		51.4		NR			0
	Metformin + sitagliptin				NR			
	Metformin + sitagliptin				NR			
Yang, 2011[180]	Metformin + placebo	56.6	52.3	C: 93, AA: 3.5, Asian:	32.5	7.97	6.2	

Author, year	Group, N	Mean age (age range),	Male, %	Race, %	Mean BMI in kg/m2 Mean weight in kg	Mean HbA1c in %	Mean duration of diabetes in years	N of withdrawals
	86			2.3, H: 40.7, O: 1.2				
	Metformin + saxagliptin 74	53.9	54.1	C: 86.5, AA: 10.8, Asian: 2.7, H: 39.2, O: 0	33.7	7.92	5.8	
Yang, 2011[181]	Metformin + glimepiride + placebo	54.1	50	NR	31.9	8.1	4	20
	Metformin + liraglutide + placebo	55.9	46	NR	32.2	8.6	4	27
	Metformin + liraglutide + placebo	54.3	44	NR	31.9	8.5	3.9	26
	Metformin + liraglutide + placebo	54.1	58	NR	30.3	8.5	3.7	38
Yang, 2012[182]	Metformin + placebo	54.5	50	NR	31.6	8.7	3.7	36
	Metformin + sitagliptin	53.9	37	NR	31.4	8.6	4.4	21
Yoon, 2011[183]	Metformin 287	54.4	48.4	Asian: 100	69.0 kg	7.9	5.1	40
	Rosiglitazone 283	53.8	48.1	Asian: 100	68.9 kg	7.9	5.1	29
	Glimepiride 231	53.6	58.4	Asian: 100	68.2 kg	8.5	7.8	
Yuan, 2012[184]	Metformin 231	53.5	54.1	Asian: 100	68.6 kg	8.5	7.4	
	Exenatide 233	53.5	54.9	Asian: 100	67.4 kg	8.6	7.5	

Abbreviations: AA = African American; BHI = biphasic human insulin; BMI = body mass index; C = Caucasian; H = Hispanic; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptidase-1; HbA1c = glycated hemoglobin; kg = kilogram; NR = NR; SU = sulfonylurea;

Some data may have not been extracted because the question was not asked.

Table D12. Results of studies evaluating safety of diabetes medications

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Agarwal, 2005[189] RCT	Grp1: Pioglitazone Varied, glucose: 140 mg/dL, HbA1c: 8% Start: 15 mg D: 16 wks Grp2: Glipizide Varied, glucose: 140 mg/dL, HbA1c: 8% Start: 5 mg D: 16 wks	Grp1: 2 events Grp2: 3 events		Grp1: 2 (2) Grp2: 2 (2)			
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: based on all reports of hypoglycemia; a concurrent glucose measurement was NOT required Grp1: 2 NA p NR Grp2: 0 NA p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c	Def: symptomatic + fingerstick glucose <=70 mg/dl Grp1: 283.4Person-years p NR Grp2: 37 283.4 Person-years p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	thresholds) ITT:No Mode of AE collection:Active Followup (wks):104						
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: symptomatic + fingerstick glucose <=50 mg/dl Grp1: 283.4Person-years p Grp2: 4 283.4 Person-years p					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104	Def: any symptomatic hypoglycemia w/ or w/o glucose measurement Grp1: 114 (22) NA p NR Grp2: 36 (7) 73 NA p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + sitagliptin + placebo	Def: symptomatic hypoglycemia and did not require documentation of a glucose measurement					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104	Grp1: 36 NA p 0.001 Grp2: 13 NA p					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104	Def: symptomatic hypogly w PG <=3.9 mmol/l Grp1: 28 (11) Person-years p NR Grp2: 86 (36) 0.47 Person-years p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: all symptomatic hypoglycemia Grp1: 35 (13) 1Person-years p Grp2: 108 (46) 4.21 1 Person-years p					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified	Def: symptomatic hypogl BG< 3.1 mmol Grp1: 12 (5) Person-					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	years p NR Grp2: 56 (24) 0.9 Person-years p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg or maximum tolerated dose) Not specified Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: total patients with hypoglycemia Grp1: 8 (5.8) NA p NR Grp2: 5 (3.6) NA p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum	Def: total patients with hypoglycemia Grp1: 8 (5.8) NA p NR Grp2: 7 (5.1) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104						
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104	Def: total patients with hypoglycemia Grp1: 8 (5.8) NA p NR Grp2: 7 (5.2) NA p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) ITT:No Mode of AE collection:Active Followup (wks):104	Def: All hypoglycaemia cases (see comments) Grp1: 5 (5.5) NA p NR Grp2: 4 (4.4) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: symptomatic hypoglycemia Grp1: 10 (3) p Grp2: 20 (6) p					
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active	Def: documented - biochemically (glucose <=3.9 mmol/l) +/- sxs Grp1: 165 (34) p Grp2: 27 (6) p <0.0001					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):104						
Ahren, 2014[2] RCT	Grp1:Metformin + glimepiride + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (2mg qdup-titration to 4mg qd if patients exceeded predefined FPG or HbA1c thresholds) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: documented - biochemically (glucose <=3.9 mmol/l) +/- sxs Grp1: 165 (34) p Grp2: 24 (5) p <0.0001					
Ahren, 2014[2] RCT	Grp1:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: diagnosis of hypoglycemia (ICD-9-CM 250.8x, diabetes with other specified manifestations; 251.0x, hypoglycemic coma; 251.1x, other specified hypoglycemia 251.2x, hypoglycemia, unspecified) on an outpatient or ER insurance claim, a principal di					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Grp1: p Grp2: 9 p					
Ahren, 2014[2] RCT	Grp1:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Ahren, 2014[2] RCT	Grp1:Metformin + sitagliptin + placebo Fixed (>=1500 mg or maximum tolerated dose) Fixed (100mg qd) Grp2:Metformin + albiglutide + placebo Fixed (>=1500 mg or maximum tolerated dose) Titrated (30mg qwup-titration to 50mg qw if patients exceeded predefined FPG or HbA1c thresholds) ITT:No Mode of AE collection:Active Followup (wks):104	Def: FPG<60mg/dl Grp1: 0 NA p NR Grp2: 0 NA p NR					
Alba, 2013[3] RCT	Grp1:Pioglitazone Fixed (30mg) Grp2:Sitagliptin	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (100mg) ITT:Yes Mode of AE collection:Active Followup (wks):12						
Amador-Licona, 2000[186] RCT	Grp1: Metformin Varied Start: 850 mg Grp2: Glibenclamide Varied Start: 5 mg					Def: Diarrhea + Diffuse abdominal pain Grp1: 4 (14.3) Grp2: NR	
Arechavaleta, 2011[5] RCT	Grp1:Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2:Metformin + sitagliptin + placebo Not specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT:No Mode of AE collection:Active Followup (wks):30	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 1 (0.9) NA p NR					
Arechavaleta, 2011[5] RCT	Grp1:Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day)	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 2 (1.8) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + sitagliptin + placebo Not specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT:No Mode of AE collection:Active Followup (wks):30						
Arechavaleta, 2011[5] RCT	Grp1:Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2:Metformin + sitagliptin + placebo Not specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT:No Mode of AE collection:Active Followup (wks):30	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 2 (3.6) NA p NR					
Arechavaleta, 2011[5] RCT	Grp1:Metformin + glimepiride + placebo Not specified (on stable metformin >=1500 mg at screening for the past 12 wks) Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day) Grp2:Metformin + sitagliptin + placebo Not specified (on at least 1500	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 3 (1.8) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	mg daily for 12 wks prior to screening at stable dose) Fixed (100mg daily) ITT:No Mode of AE collection:Active Followup (wks):30						
Arjona Ferreira, 2013[6] RCT	Grp1:Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2:Sitagliptin + placebo Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT:No Mode of AE collection:Active Followup (wks):58	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 4 (2.4) NA p NR					
Arjona Ferreira, 2013[6] RCT	Grp1:Glipizide + placebo Titrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia) Grp2:Sitagliptin + placebo	Def: plasma glucose <=70mg/dL Grp1: 1 (0.9) NA p NR Grp2: 2 (3.6) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study) ITT:No Mode of AE collection:Active Followup (wks):58						
Aschner, 2010[7] RCT	Grp1: Metformin Varied, prespecified dose Start: 500 mg, Max: 2000 mg; Mean: 1903 mg D: 5 wks Grp2: Sitagliptin Fixed Mean: 100 mg	Coll: Passive Timing: Unspecified ITT: No Grp1: Severe: 0 (0) Mild/moderate: 17 (3.3); 23 events Grp2: Severe: 2 (<1) Mild/moderate: 9 (1.7); 17 events				Def: Combined GI events; Nausea; Diarrhea; Vomiting; Abdominal pain Coll: NR Timing: Unspecified ITT: No Grp1: (20.7, 3.1, 10.9, 1.3, 3.8) Grp2: (11.6, 1.1, 3.6, 0.4, 2.1)	
Aschner, 2012[8] RCT	Grp1:Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2:Metformin + insulin	Def: plasma glucose <=70mg/dL Grp1: 2 (1.8) NA p NR Grp2: 2 (3.6) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT:No Mode of AE collection:Active Followup (wks):	NR					
Aschner, 2012[8] RCT	Grp1:Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2:Metformin + insulin glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT:No Mode of AE collection:Active Followup (wks):	Def: plasma glucose <=70mg/dL Grp1: 1 (0.9) NA p NR Grp2: 3 (1.8) NA p NR					
Aschner, 2012[8] RCT	Grp1:Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2:Metformin + insulin glargine Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT:No Mode of AE collection:Active Followup (wks):24	Def: plasma glucose <=70mg/dL Grp1: 1 (0.9) NA p NR Grp2: 4 (2.4) NA p NR					
Aschner, 2012[8] RCT	Grp1:Metformin + sitagliptin Not specified (baseline dose of metformin was 1835 mg) Fixed (100 mg) Grp2:Metformin + insulin glargine	Def: plasma glucose <=70mg/dL Grp1: 2 (1.8) NA p NR Grp2: 3 (1.8) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Not specified (mean baseline dose 1852 mg) Titrated (0.5 U/kg at 24 wks) ITT:No Mode of AE collection:Active Followup (wks):25						
Bailey, 2005[9] RCT	Grp1: Metformin Varied Start: 2500 mg, Max: 3000 mg D: 24 wks Grp2: Metformin + rosiglitazone Fixed; Varied Start: 2000 mg; Start: 4 mg, Max: 8 mg D: 24 wks	Grp1: Serious: 0, Mild or moderate: 1 (<1) Grp2: Serious: 0, Mild or moderate: 3 (1)				Def: diarrhea and abdominal pain Grp1: (5.4) Grp2: (3.2)	Def: acute cholecystitis, serious cholelithiasis and cholestatic jaundice Coll: Active Timing: Specified ITT: Yes Grp1: 1 (<1) Grp2: 0 (0)
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2:Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mgMedian: 1500 mg) Fixed (2.5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	Def: plasma glucose <=70mg/dL Grp1: 2 (1.8) NA p NR Grp2: 4 (2.4) NA p NR					
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg)	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + dapagliflozin Fixed (Mean: 1854 mgMedian: 2000 mg) Fixed (5.0 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	NR Grp2: 3 (1.8) NA p NR					
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2:Metformin + dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	Def: plasma glucose <=70mg/dL Grp1: 2 (3.6) NA p NR Grp2: 4 (2.4) NA p NR					
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2:Metformin + dapagliflozin + placebo Fixed (Mean: 1792 mgMedian: 1500 mg) Fixed (2.5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	Def: hypoglycaemia, either symptomatic or laboratory-documented Grp1: 1 NA p NR Grp2: 0 NA p NR					
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2:Metformin + dapagliflozin Fixed (Mean: 1854 mgMedian: 2000 mg) Fixed (5.0 mg) ITT:Yes	Def: hypoglycaemia, either symptomatic or laboratory-documented Grp1: 1 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):102						
Bailey, 2013[10] RCT	Grp1:Metformin + placebo Fixed (Mean: 1861 mgMedian: 1500 mg) Grp2:Metformin + dapagliflozin + placebo Fixed (Mean: 1800 mgMedian: 1500 mg) Fixed (10.0 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	Def: Unspecified AE Grp1: 2 (1.4) Persons p NR Grp2: 5 (3.6) Persons p NR					
Bakris, 2006[12] RCT	Grp1: Metformin + rosiglitazone Varied, glucose: ≤6.6 mmol/L Unclear; Start: 4 mg D: 3 wks Grp2: Metformin + glyburide Varied, glucose: ≤ 6.6 mmol/L Unclear; Start: 5 mg D: 3 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 2 (1) Grp2: 22 (12)					
Barnett, 2012[13] RCT	Grp1:Glimepiride Titrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg qd and uptitrated in 1mg increments every 4 wks to 4mg qd max if fassting blood glucose was >110mg/dl (6.1mmol/l)) Grp2:Linagliptin Fixed (5mg qdstarted this at randomization and on for all 52 wks) ITT:Yes Mode of AE collection:Active Followup (wks):34	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 3 NA p NR					
Barnett, 2012[13]	Grp1:Glimepiride	Def: Unspecified AE					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Titrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg qd and uptitrated in 1mg increments every 4 wks to 4mg qd max if fassting blood glucose was >110mg/dl (6.1mmol/l)) Grp2:Linagliptin Fixed (5mg qdstarted this at randomization and on for all 52 wks) ITT:Yes Mode of AE collection:Active Followup (wks):34	Grp1: 0 NA p NR Grp2: 0 NA p NR					
Bergenstal, 2010[14] RCT	Grp1:Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2:Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: Unspecified AE Grp1: 3 NA p NR Grp2: 0 NA p NR					
Bergenstal, 2010[14] RCT	Grp1:Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2:Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) ITT:No Mode of AE collection: NR/unclear	Def: typical symptoms of hypoglycemia that recovered after the ingestion of glucose and/or a confirmed blood glucose level < 3.3mmol/l Grp1: NA p NR Grp2: 2 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):26						
Bergenstal, 2010[14] RCT	Grp1:Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2:Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: BG < =3.0 mmol/L Grp1: (1.8) p Grp2: (6.3) p NS					
Bergenstal, 2010[14] RCT	Grp1:Metformin + pioglitazone + placebo Fixed (Mean: 1480mg) Fixed (45mg daily) Grp2:Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: Unspecified AE Grp1: 280 (36) NA p Grp2: 58 (7) NA p <0.0001					
Bergenstal, 2010[14] RCT	Grp1:Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2:Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: at least one episode of hypoglycemia reported Grp1: 338 (67) Persons p <0.0001 Grp2: 186 (36) Persons p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Bergenstal, 2010[14] RCT	Grp1:Metformin + sitagliptin + placebo Fixed (Mean: 1583mg) Fixed (100mg daily) Grp2:Metformin + exenatide + placebo Fixed (Mean: 1504mg) Fixed (2mg weekly) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: <3.9 mmol + symptomatic Grp1: 240 (47) Persons p <0.0001 Grp2: 102 (20) Persons p					
Bergenstal, 2012[15] RCT	Grp1:Metformin + placebo Fixed (Stable dose of >/=1,500mg/day) Grp2:Metformin + sitagliptin + placebo Fixed (Stable dose of >/=1,500mg/day) Fixed (100mg QD) ITT:No Mode of AE collection:Active Followup (wks):24	Def: <2.8mmol + symptomatic Grp1: 63 (12) Persons p 0.002 Grp2: 34 (7) Persons p					
Blonde, 2002[16] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Fixed Start: 10 mg	Def: Mild or moderate, Fsg≤60mg/dl + symptomatic Grp1: 1 (<1) Grp2: 3 (1.8)				Def: Dyspepsia and heartburn; Nausea + vomiting; Flatulence Grp1: (4.6); (12.4); (2) Grp2: (3); (5.5); (0)	
Blonde, 2002[16] RCT	Grp1: Metformin Varied	Def: FSG≤60mg/dl + symptomatic				Def: Dyspepsi	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg	Grp1: Mild or moderate: 1 (<1) Grp2: Mild or moderate: 22 (6.8)				a and heartburn; Nausea + vomiting; Flatulence Grp1: (4.6; 12.4; 2) Grp2: (3.7; 6.8; 2.5)	
Blonde, 2002[16] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Def: FSG≤60mg/dl + symptomatic Grp1: Mild or moderate: 1 (<1) Grp2: Mild or moderate: 22 (6.8)				Def: Dyspepsia and heartburn; Nausea + vomiting; Flatulence Grp1: (4.6; 12.4; 2) Grp2: (5; 10; 6.3)	
Bolinder, 2012[17] RCT	Grp1:Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment) Grp2:Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT: NR Mode of AE collection:Active Followup (wks):102	Def: hypoglycemic episodes Grp1: NA p NR Grp2: 4 NA p NR					
Bolinder, 2012[17]	Grp1:Metformin + placebo Fixed (Patients continued open-	Def: combination of reports of signs or					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	label metformin dosage from prior to enrollment) Grp2:Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	symptoms consistent with hypoglycemia, with or without documented glucose levels, or reported low glucose levels without symptoms Grp1: (38.4) NA p NR Grp2: (3.5) NA p NR					
Bolinder, 2012[17] RCT	Grp1:Metformin + placebo Fixed (Patients continued open-label metformin dosage from prior to enrollment) Grp2:Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):102	Def: Confirmed <50 mg/dl plasma glucose levels with associated symptoms Grp1: (9.1) NA p NR Grp2: (0) NA p NR					
Borges, 2011[18] RCT	Grp1:Metformin Titrated (Max: 2000 mg/dStart 500mg/d) Grp2:Metformin + rosiglitazone Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg) ITT:No Mode of AE collection:Active Followup (wks):80	Def: Unspecified AE Grp1: p Grp2: 3 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Cefalu, 2013[20] RCT	Grp1:Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2:Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (100mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: â€ Events consistent with hypoglycemia and with plasma glucose levels of <=3.9 mmol/L and/or requiring assistance Grp1: 1 (0.5) NA p NR Grp2: 4 (1.8) NA p NR					
Cefalu, 2013[20] RCT	Grp1:Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of	Def: Events consistent with hypoglycemia and with plasma glucose levels of <=3.9 mmol/L and/or requiring assistance Grp1: 1 (0.5) NA p NR Grp2: 3 (1.4) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	maximum approved dose in the country of the investigational site)) Grp2:Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (300mg) ITT:Yes Mode of AE collection:Active Followup (wks):52						
Cefalu, 2013[20] RCT	Grp1:Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2:Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory)	Def: None led to discontinuation from study, and none was major (defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol, Grp1: 0 (0) NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (100mg) ITT:No Mode of AE collection:Active Followup (wks):52						
Cefalu, 2013[20] RCT	Grp1:Metformin + glimepiride Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site)) Grp2:Metformin + canagliflozin Fixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory) Fixed (300mg) ITT:No Mode of AE collection:Active Followup (wks):52	Def: None led to discontinuation from study, and none was major (defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol â□„ l, Grp1: 0 (0) NA p NR Grp2: 5 (2.6) NA p NR					
Charbonnel, 2006[21] RCT	Grp1: Metformin Varied, HbA1c: 7 -10% Start: ≥1500 mg D: 19 wks Grp2: Metformin + sitagliptin Varied; Fixed Start: ≥1500 mg; Mean: 100 mg	Def: Mild or moderate Grp1: 5 (2.1) Grp2: 6 (1.3)				Def: Abdominal pain, nausea, vomiting, or diarrhea	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	D: 19 wks					Coll: NR Timing: Unspecified ITT: No Grp1: (10.5) Grp2: (11.9)	
Charpentier, 2001[22] RCT	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Glimepiride Fixed or Varied 1 mg (either fixed or increased stepwise to 2, 4, 6 mg od depending on clinical symptoms of hypoglycemia)	Def: Clinical symptoms Grp1: Serious: 0 (0), Mild or moderate: 8 (11) Grp2: Serious: 3 (2), Mild or moderate: 17 (11)				Def: Diarrhea Grp1: (7) Grp2: (1)	
Charpentier,2001[22] RCT	Grp1: Metformin Fixed Start: 850 mg tid Grp2: Metformin + glimepiride Fixed Start: 850 mg tid; Start: 1 mg	Def: Clinical symptoms Grp1: Serious: 0 (0), Mild or moderate: 8 (11) Grp2: Serious: 2 (1.4), Mild or moderate: 30 (21)				Def: diarrhea Grp1: (7) Grp2: (3)	
Chien, 2007[24] RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Mean: 1910 mg D: 4 wks Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 10 mg, Max: 20 mg, Mean: 19 mg D: 4 wks	Def: Mild or moderate Coll: Passive Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)			Def: Right metacarpal bone fracture Coll: passive Timing: Unspecified ITT: Yes	Def: Diarrhea, dry mouth, increased appetite, GI disease Coll: Passive Timing:	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
					Grp1: 0 Grp2: 1 (6)	Unspecified ITT: Yes Grp1: (32) Grp2: (13)	
Chien, 2007[24] RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Mean: 1910 mg D: 4 wks Grp2: Metformin + glyburide Varied, glucose: <140 mg/dL Start: 1000 mg, Max: 2000 mg, Mean: 1680 mg; Start: 5 mg, Max: 10 mg, Mean: 8.4 mg D: 4 wks	Def: Mild or moderate Coll: Passive Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)			Def: Right metacarpal bone fracture Coll: passive Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)	Def: Diarrhea, dry mouth, increased appetite, GI disease Coll: Passive Timing: Unspecified ITT: NR Grp1: (32) Grp2: (13)	
Comaschi, 2007[25] RCT	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: NR, 22 wks Grp2: Metformin + sulfonylurea Varied, HbA1c: 7.50% Start: 400 mg, Max: 3 g; Start: 2.5 mg D: 22 wks	Def: Mild or moderate Grp1: 0 (0) Grp2: 1 (1)					
Comaschi, 2007[25] RCT	Grp1: Metformin + pioglitazone Varied Max: 3 g; Start: 15 mg, Max: 30 mg D: NR; 22 wks Grp2: Pioglitazone +	Def: Mild or moderate Grp1: 0 (0) Grp2: 0 (0)					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	sulfonylurea Varied, HbA1c: 7.50% Start: 15 mg, Max: 30 mg; Unclear D: 22 wks; NR						
Curkendall, 2014[216] Retrospective cohort	Grp1:Metformin + su Not specified Not specified Grp2:Metformin + saxagliptin Not specified Not specified ITT:Not applicable (e.g., cohort) Mode of AE collection:Passive Followup (wks):16	Def: None led to discontinuation from study, and none was major (defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol â□„ l, Grp1: 0 NA p NR Grp2: 5 (2.6) NA p NR					
Davies, 2007[26] RCT	Grp1: Metformin + NPH Varied, glucose < 6.0 mmol/L NR; Start: 10 IU/kg; Mean: 0.58 IU/kg D: 6 wks Grp2: Metformin + BHI 70/30 Varied, glucose < 6.0 mmol/L NR; Start: 10 IU bid, Mean: 0.63 IU bid	Def: Clinical hypoglycemia Coll: Active Timing: Specified ITT: NR Grp1: (25) Grp2: (29.6)					
Davies, 2013[218] RCT	Grp1:Metformin + exenatide Fixed (met dosage prior to study (>=1000mg/day)) Fixed (2mg qweek)	Def: Unspecified AE Grp1: 6 (2.9) NA p NR Grp2: 2 (0.9) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + insulin detemir Fixed (met dosage prior to study (>=1000 mg/day)) Titrated (mean initial dose 0.21+/-0.10IU/Kg per day (20.8+/-10.8IU/day), end dose 0.51+/-0.3IU/Kg per day(50.8=5+/-28.1 IU/day).Initiated and titrated according to manufacturer labeling and a published treat-to-target titration algorithm described by Hol ITT:Yes Mode of AE collection:Active Followup (wks):26	NR					
Davies, 2013[218] RCT	Grp1:Metformin + exenatide Fixed (met dosage prior to study (>=1000mg/day)) Fixed (2mg qweek) Grp2:Metformin + insulin detemir Fixed (met dosage prior to study (>=1000 mg/day)) Titrated (mean initial dose 0.21+/-0.10IU/Kg per day (20.8+/-10.8IU/day), end dose 0.51+/-0.3IU/Kg per day(50.8=5+/-28.1 IU/day).Initiated and titrated according to manufacturer labeling and a published treat-to-target titration algorithm described by Hol ITT:Yes Mode of AE collection:Active	Def: Unspecified AE Grp1: 6 (2.9) NA p NR Grp2: 7 (3.3) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):26						
DeFronzo, 1995[27] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Glyburide Varied Start: 10 mg, Max: 20 mg	Def: Mild or moderate Grp1: 4 (2) Grp2: 6 (3)				Def: Nausea + diarrhea Grp1: (1.4) Grp2: (1)	
DeFronzo, 1995[27] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2500 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 2500 mg; Start: 10 mg, Max: 20mg	Def: Mild or moderate Grp1: 4 (2) Grp2: 38 (18)				Def: Nausea + diarrhea Grp1: (1.4) Grp2: (0.9)	
DeFronzo, 2005[28]	Grp1: Metformin + placebo Fixed >=1500 mg/d Grp2: Metformin + exenatide Fixed >=1500 mg/d Fixed 10 mcg	Def: mild Grp1: NR (5.3) Grp2: NR (4.5)				Def: diarrhea Grp1: 9(8) Grp2: 13 (12) Def: vomiting Grp1: 4(4) Grp2: 12(11) Def: nausea Grp1: 26(23) Grp2: 40(36)	
DeFronzo, 2005[28]	Grp1: Metformin + placebo Fixed >=1500 mg/d Grp2: Metformin + exenatide Fixed >=1500 mg/d Fixed 20 mcg	Def: mild Grp1: NR (5.3) Grp2: NR (5.3)				Def: diarrhea Grp1:9 (8) Grp2: 18 (16) Def: vomiting	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						Grp1: 4(4) Grp2: 13(12) Def: nausea Grp1: 26(23) Grp2: 51(45)	
DeFronzo, 2009[29] RCT	Grp1: Metformin Fixed Grp2: Metformin + saxagliptin Fixed NR; Mean: 10 mg	Grp1: Severe: 1 (1) Mild/moderate: 9 (5) Grp2: Severe: 1 (1) Mild/moderate: 7 (4)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 20 (11) Grp2: 10 (6)	
DeFronzo, 2009[29] RCT	Grp1: Metformin Fixed Grp2: Metformin + saxagliptin Fixed NR; Mean: 5 mg	Grp1: Severe: 1 (1) Mild/moderate: 9 (5) Grp2: Severe: 1 (1) Mild/moderate: 10 (5)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 20 (11) Grp2: 11 (6)	
DeFronzo, 2009[29] RCT	Grp1: Metformin Fixed Grp2: Metformin + saxagliptin Fixed	Grp1: Severe: 1 (1) Mild/moderate: 9 (5) Grp2: Severe: 1 (1) Mild/moderate:				Def: Diarrhea Coll: Active	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	NR; Mean: 2.5 mg	15 (8)				Timing: Unspecified ITT: Yes Grp1: 20 (11) Grp2: 19 (10)	
Defronzo, 2010[30] RCT	Grp1: Metformin + rosiglitazone Varied, prespecified dose NR: Start: 4 mg; Max: 8 mg Grp2: Metformin + exenatide Varied, prespecified dose NR: Start: 0.010 mg; Max: 0.02 mg BID D: 2 months	Coll: NR Timing: Unspecified ITT: No Grp1: Severe: 0 (0); Mild/moderate: 0 (0) Grp2: Severe: 0 (0); Mild/moderate: 2 (4)				Def: Vomiting; Diarrhea Coll: NR Timing: Unspecified ITT: No Grp1: (0; 9) Grp2: (49; 16)	
Del Prato, 2015[32]	Grp1: Metformin + glipizide Titrated 5,10,20mg Grp2: Metformin + dapagliflozin Titrated 2,5,20mg	Grp1: Mild:200 (49) Grp2: Mild:15 (3.7) Grp1: Severe: 3 (0.7) Grp2: Severe: 0 (0)				Def: Diarrhea Grp1: 10.3 Grp2: 8.6 Def: Nausea Grp1: 4.7 Grp2: 4.9 Def: Abdominal pain Grp1: 3.4 Grp2: 4.4 Def: Dyspepsi	Def: Unspecified AE Grp1: 7.8 Grp2: 11.8 Def: Confirmed UTI Grp1: 9.9 Grp2: 13.5 Def: eGFR decreased

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						a Grp1: 4.9 Grp2: 4.4	Grp1: 3 (0.7) Grp2: 2 (0.5) Def: Renal impairment Grp1: 11 (2.7) Grp2: 10 (2.5) Def: Reduced creatinine clearance Grp1: 13 (3.2) Grp2: 20 (4.9) Def: Vulvovaginal candidiasis Grp1: 3 (0.7) Grp2: 18 (4.4) Def: Confirmed genital infection Grp1: 12 (2.9) Grp2: 58 (14.3)

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Del Prato, 2014[33]	Grp1: Metformin + glipizide Titrated 1823.4 mg Titrated 5 mg Grp2: Metformin + alogliptin Titrated 1825.2 mg Fixed 12.5 mg	Def: total - unspecified Grp1: NR(23.2) Grp2: NR(2.5) Def: severe Grp1: NR(0.6) Grp2:NR(0.1) Def: total - spontaneous reporting Grp1: NR(10.5) Grp2: NR(2.1)				Def: diarrhea Grp1: NR(7.2) Grp2: NR(6.9)	Def: pancreatitis Grp1: NR(0.3) Grp2: NR(0)
Del Prato, 2014[33]	Grp1: Metformin + glipizide Titrated 1823.4 mg Titrated 5 mg Grp2:Metformin + alogliptin Titrated 1837.2 mg Fixed 25 mg	Def: total – unspecified Grp1: NR(23.2) Grp2: NR(1.4) Def: severe Grp1: NR(0.6) Grp2: NR(0) Def: total – spontaneous reporting Grp1: NR10.5) Grp2: NR(0.7)				Def: diarrhea Grp1: NR(7.2) Grp2: NR(6.8)	Def: pancreatitis Grp1: NR(0.3) Grp2: NR(0.1)
Derosa, 2004[34] RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glimepiride Varied Start: 1 mg, Max: 4 mg	Grp1: 0 (0) Grp2: 0 (0)				Def: Nausea + diarrhea Grp1: 2 (2.4) Grp2: NR	
Derosa, 2005[36] RCT	Grp1: Metformin + rosiglitazone Fixed Start dose: 500 mg tid, Max: 500 mg tid; Start dose: 4mg, Max: 4 mg Grp2: Metformin + glimepiride Fixed		Def: Transiently elevated LFT to 1.5 times				

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start dose: 500 mg tid, Max: 500 mg tid; Start dose: 2 mg, Max: 2 mg		upper limit of normal Coll: NR Timing: Unspecified ITT: NR Grp1: 3 events out of 48 participants Grp2: NR				
Derosa, 2005[37] RCT	Grp1: Metformin + rosiglitazone Fixed Start: 1500 mg; Start: 4 mg Grp2: Metformin + glimepiride Fixed Start: 1500 mg; Start: 2 mg					Def: Transient flatulence Grp1: (4.2) Grp2: (2.1)	
Derosa, 2010[39] RCT	Grp1: Metformin + glibenclamide NR Mean: 1500 mg; Start: 7.5 mg; Max: 15 mg Grp2: Metformin + exenatide NR NR; Start: 10 mcg; Max: 20 mcg	Def: FPG < 60 mg/dL Coll: Active Timing: Specified ITT: No Grp1: 3 (5) Grp2: 0 (0)				Def: Vomiting; Diarrhea Coll: Active Timing: Specified ITT: No Grp1: (2; 2) Grp2: (2; 3)	
Derosa, 2013[42] RCT	Grp1:Metformin + placebo Fixed (2500+/-500mg/day as	Def: Unspecified AE Grp1: 2 (0.9) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	previously determined during run-in period) Grp2:Metformin + sitagliptin Fixed (2500+/-500mg/day as previously determined during run-in period) Fixed (100mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):48	NR Grp2: 7 (3.3) NA p NR					
Derosa, 2013[43] RCT	Grp1:Metformin + placebo Fixed (Mean: 2500 +/- 500mg titrated up during run-in for 8+/- 2 months) Grp2:Metformin + exenatide Fixed (Mean: 2500 +/- 500mg titrated up during run-in over 8+/- 2 months) Titrated (Max: 20 ug daily5ug b.i.d. for the first 4 wks and then 10 ug b.i.d. thereafter) ITT:No Mode of AE collection:Active Followup (wks):48	Def: Hypoglycaemic events were defined as: an episode with symptoms and confirmed low glucose; an episode with low glucose; or an episode with symptoms when glucose was not measured Grp1: 10 (6.8) 147Persons p Grp2: 3 (2.2) 139 Persons p					
Diamant, 2010[44] RCT	Grp1:Metformin + exenatide Not specified (continued stable dose) Fixed (2mg weekly) Grp2:Metformin + insulin glargine Not specified (continued stable dose) Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L)	Def: Unspecified AE Grp1: 0 Persons p NR Grp2: 0 Persons p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:Yes Mode of AE collection: NR/unclear Followup (wks):26						
Diamant, 2010[44] RCT	Grp1:Metformin + exenatide Not specified (continued stable dose) Fixed (2mg weekly) Grp2:Metformin + insulin glargine Not specified (continued stable dose) Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):26	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Diamant, 2010[44] RCT	Grp1:Metformin + exenatide Not specified (continued stable dose) Fixed (2mg weekly) Grp2:Metformin + insulin glargine Not specified (continued stable dose) Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT:No Mode of AE collection: NR/unclear Followup (wks):84	Def: documented plasma or fingerstick <=3.9 mmol/l or severe requiring assistance Grp1: Persons p Grp2: (4.1) Persons p					
Diamant, 2010[44] RCT	Grp1:Metformin + exenatide Not specified (continued stable dose)	Def: documented plasma or fingerstick <=3.9 mmol/l or					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (2mg weekly) Grp2:Metformin + insulin glargine Not specified (continued stable dose) Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L) ITT:No Mode of AE collection: NR/unclear Followup (wks):84	severe requiring assistance Grp1: Persons p Grp2: (6.8) Persons p					
Dormuth, 2009[219] Cohort	Grp1: Thiazolidinedione NR Grp2: Sulfonylurea NR				Def: Hip fractures Coll: Passive Timing: Unspecified ITT: NA Grp1: HR: 1.28 (CI: 1.12 to 1.45) Grp2: ref		
Einhorn, 2000[45] RCT	Grp1: Metformin NR Grp2: Metformin + pioglitazone NR; Fixed NR; 30 mg	Grp1: 1 (0.6) Grp2: 1 (0.6)					
Erem, 2014[47] RCT	Grp1:Metformin Titrated (Max: 2000mg4-8 wks of titration then fixed after that - article reported all patients ended up on 2000 mg) Grp2:Pioglitazone Titrated (Max: 45mg according	Def: documented plasma or fingerstick <=3.9 mmol/l or severe requiring assistance Grp1: Persons p Grp2: (6.8)					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	to glycemic controlinitiated at 15mg/day and titrated in first 4-8 wks then fixed after that (ended up 6 pts on 15 mg, 12 pts on 30 mg and 1 pt on 45 mg)) ITT:No Mode of AE collection: NR/unclear Followup (wks):48	Persons p					
Feinglos, 2005[52] RCT	Grp1: Metformin Fixed Start: ≥1000 mg Grp2: Metformin + glipizide Fixed Start: ≥1000 mg; 2.5 mg	Def: FSG <60 mg/dl w/ symptoms or FSG <50 mg/dl w/o symptoms or FPG<55 mg/dl w/o symptoms Grp1: Serious: 0, Mild or moderate: 2 (3.3) Grp2: Serious: 0, Mild or moderate: 9 (14.8)					
Ferrannini, 2013[53] RCT	Grp1:Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2:Empagliflozin Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: documented plasma or fingerstick <=3.9 mmol/l or severe requiring assistance Grp1: (4.1) Persons p Grp2: (6.8) Persons p					
Ferrannini, 2013[53] RCT	Grp1:Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2:Empagliflozin Fixed (25 mg)	Def: documented plasma or fingerstick <=3.9 mmol/l or severe requiring assistance Grp1: (4.1) Persons					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:No Mode of AE collection:Active Followup (wks):78	p Grp2: (6.8) Persons p					
Ferrannini, 2013[53] RCT	Grp1:Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2:Metformin + sitagliptin Not specified Fixed (100 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: Unspecified AE Grp1: (9) NA p NR Grp2: (10) 6 NA p NR					
Ferrannini, 2013[53] RCT	Grp1:Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2:Metformin + empagliflozin Not specified Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: Unspecified AE Grp1: (9) NA p NR Grp2: (6) 3 NA p NR					
Ferrannini, 2013[53] RCT	Grp1:Metformin Fixed (Max: maximum of 1,000 mg twice daily or the maximum tolerated dose) Grp2:Metformin + empagliflozin Not specified Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: withdrawal due to hypoglycemia Grp1: 0 NA p NR Grp2: 1 NA p NR					
Ferrannini, 2013[53] RCT	Grp1:Empagliflozin Fixed (10 mg) Grp2:Metformin + sitagliptin Not specified	Def: events consistent with signs and symptoms of hypoglycemia with					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (100 mg) ITT:No Mode of AE collection:Active Followup (wks):78	or without documented blood glucose levels Grp1: 20 (6.1) NA p NR Grp2: 7 (2.1) NA p NR					
Ferrannini, 2013[53] RCT	Grp1:Empagliflozin Fixed (25 mg) Grp2:Metformin + sitagliptin Not specified Fixed (100 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: events consistent with signs and symptoms of hypoglycemia with or without documented blood glucose levels Grp1: 20 (6.1) NA p NR Grp2: 15 (4.7) NA p NR					
Ferrannini, 2013[53] RCT	Grp1:Empagliflozin Fixed (10 mg) Grp2:Metformin + empagliflozin Not specified Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: events consistent with signs and symptoms of hypoglycemia with or without documented blood glucose levels Grp1: 20 (6.1) NA p NR Grp2: 22 (6.8) NA p NR					
Ferrannini, 2013[53] RCT	Grp1:Empagliflozin Fixed (10 mg) Grp2:Metformin + empagliflozin Not specified Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: events consistent with signs and symptoms of hypoglycemia with or without documented blood glucose levels Grp1: 7 (2.1) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		NR Grp2: 15 (4.7) NA p NR					
Ferrannini, 2013[53] RCT	Grp1:Empagliflozin Fixed (25 mg) Grp2:Metformin + empagliflozin Not specified Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: events consistent with signs and symptoms of hypoglycemia with or without documented blood glucose levels Grp1: 7 (2.1) NA p NR Grp2: 22 (6.8) NA p NR					
Ferrannini, 2013[53] RCT	Grp1:Empagliflozin Fixed (25 mg) Grp2:Metformin + empagliflozin Not specified Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: documented hypoglycemia (oncurrent fingerstick or plasma glucose <= 3.9 mmol/L with or without symptoms) Grp1: (3.2) NA p NR Grp2: (4.3) NA p NR					
Ferrannini, 2013[53] RCT	Grp1:Metformin + sitagliptin Not specified Fixed (100 mg) Grp2:Metformin + empagliflozin Not specified Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Def: documented hypoglycemia (oncurrent fingerstick or plasma glucose <= 3.9 mmol/L with or without symptoms) Grp1: (3.2) NA p NR Grp2: (3.2) NA p NR					
Ferrannini,	Grp1:Metformin + sitagliptin	Def: Unspecified AE					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
2013[53] RCT	Not specified Fixed (100 mg) Grp2:Metformin + empagliflozin Not specified Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):78	Grp1: 23 (3.7) NA p NR Grp2: 19 (3) NA p NR					
Ferrannini, 2013[194] RCT	Grp1:Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2:Empagliflozin Fixed (10mg) ITT:No Mode of AE collection: NR/unclear Followup (wks):12	Def: confi rmed hypoglycaemic adverse events (plasma glucose â‰¤3Â·9 mmol/L or requiring assistance) Grp1: 189 (24) Persons p NR Grp2: 19 (2) Persons p NR					
Ferrannini, 2013[194] RCT	Grp1:Metformin Titrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose) Grp2:Empagliflozin Fixed (25mg) ITT:No Mode of AE collection: NR/unclear Followup (wks):12	Def: â€ Confi rmed events, plasma glucose <3Â·9 mmol/L or requiring assistance, or both Grp1: NA p NR Grp2: 1 NA p NR					
Fonseca, 2000[55] RCT	Grp1: Metformin Fixed Start: 2500 mg Grp2: Metformin + rosiglitazone Fixed	Def: mild or moderate Grp1: 2 (2) Grp2: 5 (4)					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 2500 mg; Start: 4-8 mg						
Fonseca, 2012[56] RCT	Grp1:Metformin Titrated (Max: 2000 mg/duptitration from 1500 to 2000 mg/d) Grp2:Metformin + saxagliptin Fixed (1500 mg/d) Fixed (5mg/d) ITT:No Mode of AE collection:Active Followup (wks):18	Def: â€ Confi rmed events, plasma glucose <3Â·9 mmol/L or requiring assistance, or both Grp1: NA p NR Grp2: 1 NA p NR					
Fonseca, 2012[56] RCT	Grp1:Metformin Titrated (Max: 2000 mg/duptitration from 1500 to 2000 mg/d) Grp2:Metformin + saxagliptin Fixed (1500 mg/d) Fixed (5mg/d) ITT:No Mode of AE collection:Active Followup (wks):18	Def: Symptomatic of hypoglycemic events Grp1: 1 (2) NA p NR Grp2: 3 (5) NA p NR					
Forst, 2010[57] RCT	Grp1:Metformin + placebo Fixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2:Metformin + glimepiride Fixed Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) ITT:Yes Mode of AE collection:Passive Followup (wks):12	Def: Symptomatic of hypoglycemic events Grp1: 1 (2) NA p NR Grp2: 1 (2) NA p NR					
Forst, 2010[57] RCT	Grp1:Metformin + placebo Fixed (17of 70 patients	Def: Symptomatic of hypoglycemic events					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	receiving <1500 mg and 53 of 70 receiving >=1500 mg) Grp2:Metformin + linagliptin Fixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT:Yes Mode of AE collection:Passive Followup (wks):12	Grp1: 1 (2) NA p NR Grp2: 4 (6) NA p NR					
Forst, 2010[57] RCT	Grp1:Metformin + glimepiride Fixed Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion) Grp2:Metformin + linagliptin Fixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin) Fixed (5mg) ITT:Yes Mode of AE collection:Passive Followup (wks):12	Def: Symptomatic of hypoglycemic events Grp1: 1 (2) NA p NR Grp2: 0 (0) NA p NR					
Forst, 2014[59] RCT	Grp1:Metformin + glimepiride Not specified Titrated (individually titrated in the range of 1-4mg to achieve best possible glycemic control as judged by the investigator) Grp2:Metformin + linagliptin Not specified Fixed (5mg) ITT:No Mode of AE collection:Active Followup (wks):12	Def: Symptomatic of hypoglycemic events Grp1: 3 (5) NA p NR Grp2: 1 (2) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Forst, 2014[59] RCT	Grp1:Metformin + glimepiride Not specified Titrated (individually titrated in the range of 1-4mg to achieve best possible glycemic control as judged by the investigator) Grp2:Metformin + linagliptin Not specified Fixed (5mg) ITT:No Mode of AE collection:Active Followup (wks):12	Def: Symptomatic of hypoglycemic events Grp1: 3 (5) NA p NR Grp2: 4 (6) NA p NR					
Gallwitz, 2011[60] RCT	Grp1:Metformin + exenatide Fixed (Median: 2000mgcontinued at prestudy dose) Titrated (Max: 20 micrograms/daystart 5ugBID 4 w then 10ug) Grp2:Metformin + insulin aspart 70/30 Not specified (Median: 2000mgcontinued at prestudy dose) Titrated (Mean: 28.4 IU/dayto reach glucose target of 5.0 -7.2 mmol/L; titrated "without a structured insulin dosing algorithm") ITT:No Mode of AE collection:Active Followup (wks):26	Def: Symptomatic of hypoglycemic events Grp1: 3 (5) NA p NR Grp2: 0 (0) NA p NR					
Gallwitz, 2011[60] RCT	Grp1:Metformin + exenatide Fixed (Median: 2000mgcontinued at prestudy dose) Titrated (Max: 20	Def: Defined by preferred MedDRA terms Grp1: (0) NA p NR Grp2: (2.8) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	micrograms/daystart 5ugBID 4 w then 10ug) Grp2:Metformin + insulin aspart 70/30 Not specified (Median: 2000mgcontinued at prestudy dose) Titrated (Mean: 28.4 IU/dayto reach glucose target of 5.0 -7.2 mmol/L; titrated "without a structured insulin dosing algorithm") ITT:No Mode of AE collection:Active Followup (wks):26	NR					
Gallwitz, 2012[61] RCT	Grp1:Metformin + glimepiride + placebo Fixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2:Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):104	Def: Defined by preferred MedDRA terms Grp1: (0) NA p NR Grp2: (0) NA p NR					
Gallwitz, 2012[61] RCT	Grp1:Metformin + glimepiride + placebo Fixed (stable dose of 1500mg	Def: Defined by preferred MedDRA terms					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	per day or more (or a maximum tolerated dose less than 1500mg per day)) Titrated (Mean: 3.0 mgMax: 4 mg once daily) Grp2:Metformin + linagliptin + placebo Fixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day)) Fixed (5 mg once daily) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):104	Grp1: (0) NA p NR Grp2: (0) NA p NR					
Gallwitz, 2012[62] RCT	Grp1:Metformin + glimepiride Not specified (Mean: 1989 mg) Titrated (Mean: 2.01 mginitial dose 1 mg; could be titrated per attending physician every 4 wks based on maximum tolerated dose and country guidelines) Grp2:Metformin + exenatide Not specified (Mean: 1956 mg) Titrated (Mean: 17.35 micgrogramsMax: 20 microgramsstarted at 5 microgm bid and titrated if possible based on GI sxs) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):	Def: Defined by preferred MedDRA terms Grp1: (2.8) NA p NR Grp2: (0) NA p NR					
Gallwitz, 2012[62] RCT	Grp1:Metformin + glimepiride Not specified (Mean: 1989 mg) Titrated (Mean: 2.01 mginitial	Def: Defined by preferred MedDRA terms					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	dose 1 mg; could be titrated per attending physician every 4 wks based on maximum tolerated dose and country guidelines) Grp2:Metformin + exenatide Not specified (Mean: 1956 mg) Titrated (Mean: 17.35 micgrogramsMax: 20 microgramsstarted at 5 microgm bid and titrated if possible based on GI sxs) ITT:No Mode of AE collection: NR/unclear Followup (wks):	Grp1: (2.8) NA p NR Grp2: (0) NA p NR					
Gallwitz, 2012[62] RCT	Grp1:Metformin + glimepiride Not specified (Mean: 1989 mg) Titrated (Mean: 2.01 mginitial dose 1 mg; could be titrated per attending physician every 4 wks based on maximum tolerated dose and country guidelines) Grp2:Metformin + exenatide Not specified (Mean: 1956 mg) Titrated (Mean: 17.35 micgrogramsMax: 20 microgramsstarted at 5 microgm bid and titrated if possible based on GI sxs) ITT:No Mode of AE collection: NR/unclear Followup (wks):	Def: symptomatic but not confirmed by measurement Grp1: 10 (4.1) p Grp2: 6 (3.7) p					
Gallwitz, 2012[62] RCT	Grp1:Metformin + glimepiride Not specified (Mean: 1989 mg) Titrated (Mean: 2.01 mginitial dose 1 mg; could be titrated per	Def: symptomatic but not confirmed by measurement Grp1: 10 (4.1) p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	attending physician every 4 wks based on maximum tolerated dose and country guidelines) Grp2:Metformin + exenatide Not specified (Mean: 1956 mg) Titrated (Mean: 17.35 micgrogramsMax: 20 microgramsstarted at 5 microgm bid and titrated if possible based on GI sxs) ITT:No Mode of AE collection: NR/unclear Followup (wks):	Grp2: 5 (3.1) p					
Garber, 2002[63] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 mg, Max: 10mg	Def: Mild or moderate Grp1: 0 (0) Grp2: 10 (6)				Def: Nausea + vomiting + diarrhea + dyspepsia Grp1: (43) Grp2: (24)	
Garber, 2002[63] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg; Start: 1.25 mg	Def: Mild or moderate Grp1: NR Grp2: 18 (11.4)				Def: Nausea + vomiting + diarrhea + dyspepsia Grp1: IR - 43 Grp2: IR - 32	
Garber, 2002[63] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 500 mg; Start: 2.5 mg	Def: Mild or moderate Grp1: NR Grp2: 61 (37.7)				Def: Nausea + vomiting + diarrhea + dyspepsia Grp1: IR - 43	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						Grp2: IR - 38	
Garber, 2003[64] RCT	Grp1: Metformin Varied Start: 500 mg (adjusted to patient response), Max: 2000 mg Grp2: Glyburide Varied Start: 2.5 (adjusted to patient response), Max: 10 mg	Def: Mild or moderate Grp1: Symptomatic: 29 (17.7), Fingerstick: 1 (0.6) Grp2: Symptomatic: 98 (57.6), Fingerstick: 16 (10.6)				Def: Abdominal pain; Nausea & Vomiting; Diarrhea Grp1: (6.1; 10.4; 18.3) Grp2: (4; 6.6; 5.3)	
Garber, 2003[64] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glyburide Varied Start: 250 mg, Max: 1000 mg; Start: 1.25 mg, Max: 5 mg	Def: Mild or moderate Grp1: Symptomatic: 29 (17.7), Fingerstick: 1 (0.6) Grp2: Symptomatic: 59 (39.1), Fingerstick: 19 (11.2)				Def: Abdominal pain; nausea + vomiting; Diarrhea Grp1: (6.1; 10.4; 18.3) Grp2: (4.1; 4.7; 7.6)	
Garber, 2006[65] RCT	Grp1: Metformin + rosiglitazone Varied Start: 1500 or 2000 mg, Max: 2000 mg; Start: 4 mg, Max: 8 Grp2: Metformin + glibenclamide Varied Start: 1000 mg, Max: 2000; Start: 5 mg , Max: 10 mg	Grp1: Severe: 0 (0), Mild or moderate: 2 (1) Grp2: Severe: 7 (4), Mild or moderate: 53 (33)				Def: Diarrhea + abdominal pain + other GI symptoms ; Diarrhea; Abdominal pain Grp1: (10;	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						3; 4) Grp2: (11; 6; 6)	
Garber, 2009[66] RCT	Grp1: Glimepiride Varied, prespecified dose Start: 2 mg, Max: 8 mg D: 2 wks Grp2: Liraglutide Varied, prespecified dose Start: 0.6 mg, Max 1.8 mg D: 2 wks	Def: Not requiring assistance, PG < 3.1 mmol/L Coll: NR Timing: Unspecified ITT: No Grp1: 24 events Grp2: 8 events				Def: Total GI events; Nausea and vomiting Coll: Passive Timing: Unspecified ITT: No Grp1: (26, 51) Grp2: (12, 38)	Def: Pancreatitis Coll: Passive Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 1 (<1)
Garber, 2009[66] RCT	Grp1: Glimepiride Varied, prespecified dose Start: 2 mg, Max: 8 mg D: 2 wks Grp2: Liraglutide Varied, prespecified dose Start: 0.6 mg, Max 1.2 mg D: 2 wks	Def: Not requiring assistance, PG < 3.1 mmol/L Coll: NR Timing: Unspecified ITT: No Grp1: 24 events Grp2: 12 events				Def: Total GI events; Nausea and vomiting Coll: Passive Timing: Unspecified ITT: No Grp1: (26, 49) Grp2: (12, 39)	Def: Pancreatitis Coll: Passive Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 1 (<1)
Garber, 2011[67] RCT	Grp1:Glimepiride + placebo Titrated (Max: 8mg) Grp2:Liraglutide + placebo Titrated (Max: 1.2 mg)	Def: symptomatic but not confirmed by measurement Grp1: 10 (4.1) p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:Yes Mode of AE collection:Active Followup (wks):104	Grp2: 13 (5.2) p					
Garber, 2011[67] RCT	Grp1:Glimepiride + placebo Titrated (Max: 8mg) Grp2:Liraglutide + placebo Titrated (Max: 1.8 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic but not confirmed by measurement Grp1: 6 (3.7) p Grp2: 5 (3.1) p					
Garber, 2011[67] RCT	Grp1:Glimepiride + placebo Titrated (Max: 8mg) Grp2:Liraglutide + placebo Titrated (Max: 1.2 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic but not confirmed by measurement Grp1: 6 (3.7) p Grp2: 13 (5.2) p					
Garber, 2011[67] RCT	Grp1:Glimepiride + placebo Titrated (Max: 8mg) Grp2:Liraglutide + placebo Titrated (Max: 1.8 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic but not confirmed by measurement Grp1: 5 (3.1) p Grp2: 13 (5.2) p					
Genovese, 2013[69] RCT	Grp1:Metformin Titrated (starting dose of 850mg/day, up-titrated to 1700mg or 2550mg in later visits depending on the glycemic response) Grp2:Pioglitazone + placebo Titrated (Max: 45mgstarting dose of 30mg qd, up-titrated to 45mg qd in later visits in the case of poor response) ITT:No Mode of AE collection:	Def: BG < 60mg/dl Grp1: 5 Persons p Grp2: 6 Persons p NS					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	NR/unclear Followup (wks):16						
Goke, 2010[70] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: Unspecified AE Grp1: (8) NA p no statistically significant difference between groups' Grp2: (4) 1 NA p					
Goke, 2010[70] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: Total hypoglycemia was defined as plasma glucose <=70 mg/dL (3.9 mmol/L) and/or symptoms and/or signs attributable to hypoglycemia. Total hypoglycemia included events that were documented symptomatic, documented asymptomatic, probable, and/or s Grp1: (12.7) Persons p NR Grp2: (11.1) Persons p NR					
Goke, 2010[70] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day)	Def: Total hypoglycemia was defined as plasma glucose <=70 mg/dL (3.9 mmol/L) and/or					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT:Yes Mode of AE collection:Active Followup (wks):104	symptoms and/or signs attributable to hypoglycemia. Total hypoglycemia included events that were documented symptomatic, documented asymptomatic, probable, and/or s Grp1: (12.7) Persons p NR Grp2: (12.3) Persons p NR					
Goke, 2010[70] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: Total hypoglycemia was defined as plasma glucose <=70 mg/dL (3.9 mmol/L) and/or symptoms and/or signs attributable to hypoglycemia. Total hypoglycemia included events that were documented symptomatic, documented asymptomatic, probable, and/or s Grp1: 1Person-years p NR Grp2: 0.47 1 Person-years p NR					
Goke, 2010[70] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7	Def: Total hypoglycemia was defined as plasma glucose <=70 mg/dL					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	mg/dayMax: 20 mg/day) Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT:Yes Mode of AE collection:Active Followup (wks):104	(3.9 mmol/L) and/or symptoms and/or signs attributable to hypoglycemia. Total hypoglycemia included events that were documented symptomatic, documented asymptomatic, probable, and/or s Grp1: 1Person-years p NR Grp2: 0.89 1 Person-years p NR					
Goke, 2010[70] RCT	Grp1:Metformin + glipizide Fixed (>/= 1500 mgMean: 1883 mg) Titrated (Mean: 14.7 mg/dayMax: 20 mg/day) Grp2:Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg) Fixed (5 mg Γüä day) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: presented to an emergency room or hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8, 251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2) Grp1: 27 p Grp2: 53 p					
Goldstein, 2003[71] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glipizide Varied Start: 30 mg, Max: 30 mg					Def: Diarrhea Grp1: (17.3) Grp2: (13.1)	
Goldstein, 2003[71]	Grp1: Metformin Varied					Def: Diarrhea	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Start: 500 mg, Max: 2000 mg Grp2: Metformin + glipizide Varied Start: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg					Grp1: (17.3) Grp2: (13.1)	
Goldstein, 2007[72] RCT	Grp1: Metformin Varied, prespecified target Start: 500 mg, Max: 2000 mg Grp2: Sitagliptin Varied, prespecified target Start: 50 mg, Max: 100 mg	Grp1: 3 (2) Grp2: 1 (1)					
Goldstein, 2007[72] RCT	Grp1: Metformin Fixed Start: 500 mg or 1000 mg bid Grp2: Metformin + sitagliptin Fixed Start: 500 mg or 1000 mg bid; Start: 50 mg bid	Def: Mild or moderate Grp1: 3 (2) Grp2: 6 (3)					
Gomez-Perez, 2002[73] RCT	Grp1: Metformin Fixed Start: 2.5 g Grp2: Metformin + rosiglitazone Fixed Start: 2.5 g; Start: 2-4 mg bid					Def: Nausea + vomiting + diarrhea + flatulence and abdominal pain Grp1: (15.4) Grp2: (16.8)	
Gupta, 2013[76] RCT	Grp1:Glimepiride Titrated (Max: 4mg/day) Grp2:Sitagliptin Titrated (Max: 200mg/day) ITT: NR Mode of AE collection: NR/unclear	Def: presented to an emergency room or hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8, 251.0, 251.1, 251.2					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):24	or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2) Grp1: 29 p Grp2: 109 p					
Haak, 2012[77] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Linagliptin Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: presented to an emergency room or hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8, 251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2) Grp1: 27 p p					
Haak, 2012[77] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Linagliptin Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: presented to an emergency room or hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8, 251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2) Grp1: 29 p p					
Haak, 2012[77] RCT	Grp1:Metformin Fixed (1000 mg)	Def: presented to an emergency room or					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Linagliptin Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8, 251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2) Grp1: 53 p p					
Haak, 2012[77] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Linagliptin Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: presented to an emergency room or hospital with an admission diagnosis of hypoglycemia: (ICD-9 codes 250.8, 251.0, 251.1, 251.2 or 962.3; ICD-10 codes E10.63, E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2) Grp1: 109 p p					
Haak, 2012[77] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 5 (2.8) NA p NR Grp2: 2 (1.1) NA p NR					
Haak, 2012[77] RCT	Grp1:Metformin Fixed (1000 mg)	Def: Unspecified AE Grp1: 3 (1.6) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Grp2: 2 (1.1) NA p NR					
Haak, 2012[77] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 4 (2.2) NA p NR Grp2: 2 (1.1) NA p NR					
Haak, 2012[77] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 5 (2.8) NA p NR Grp2: 5 (2.6) NA p NR					
Haak, 2012[77] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 5 (2.8) NA p NR Grp2: 9 (4.9) NA p NR					
Haak, 2012[77] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active	Def: Unspecified AE Grp1: 3 (1.6) NA p NR Grp2: 5 (2.6) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):24						
Haak, 2012[77] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 3 (1.6) NA p NR Grp2: 9 (4.9) NA p NR					
Haak, 2012[77] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 4 (2.2) NA p NR Grp2: 5 (2.6) NA p NR					
Haak, 2012[77] RCT	Grp1:Linagliptin Fixed (5 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 4 (2.2) NA p NR Grp2: 9 (4.9) NA p NR					
Haak, 2012[77] RCT	Grp1:Linagliptin Fixed (5 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: Unspecified AE Grp1: 2 (1.1) NA p NR Grp2: 5 (2.6) NA p NR					
Haak, 2012[77] RCT	Grp1:Linagliptin Fixed (5 mg) Grp2:Metformin + linagliptin Fixed (1000 mg)	Def: Unspecified AE Grp1: 2 (1.1) NA p NR Grp2: 9 (4.9) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	NR					
Haak, 2012[77] RCT	Grp1:Linagliptin Fixed (5 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: symptoms only Grp1: Person-years p NR Grp2: 0.18 Person-years p NR					
Haak, 2013[78] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: symptoms only Grp1: Person-years p NR Grp2: 0.18 Person-years p NR					
Haak, 2013[78] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: symptoms only Grp1: Person-years p NR Grp2: 0.16 Person-years p NR					
Haak, 2013[78] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Fixed (1000 mg) Fixed (5.0 mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: symptomatic or biochemica Grp1: 3 (1.5) p Grp2: 1 (0.5) p					
Haak, 2013[78]	Grp1:Metformin	Def: symptomatic					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Titrated (Max: 2000 mg) Grp2:Metformin + linagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	hypoglycemia - presence of typical adrenergic or neuroglycopenic symptoms and signs, regardless of the data for self-monitoring of blood glucose Grp1: (3.51) p 0 Grp2: (6.84) 8 p NS					
Hamann, 2008[80] RCT	Grp1: Metformin + rosiglitazone Varied, glucose: 6.1 mmol/l Max: 2 g; Start: 4 mg, Max: 8 mg D: 12 wks Grp2: Metformin + sulfonylurea Varied, glucose: 6.1 mmol/l Max: 2 g; Start: 5 mg, Max: 15 mg D: 12 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 18 (6) Grp2: 90 (30)				Coll: Active Timing: Specified ITT: Yes Grp1: (13) Grp2: (18)	
Hanefeld, 2004[81] RCT	Grp1: Metformin + sulfonylurea Varied; Fixed Start: 850 mg, Max: 2550 mg; NR D: 12 wks Grp2: Pioglitazone + sulfonylurea Varied; Fixed Start: 15 mg (, Max: 45 mg; NR D: 12 wks	Def: Serious Grp1: 0 (0) Grp2: 0 (0)				Def: Diarrhea Grp1: (12.2) Grp2: (23.4)	
Hanefeld, 2007[82] RCT	Grp1: Rosiglitazone Fixed Start: 4 mg Grp2: Glibenclamide Varied	Coll: NR Timing: Unspecified ITT: Yes Grp1: 1 (0.5) Grp2: Serious: 2				Def: Unspecified Coll: NR Timing:	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 2.5 mg, Max: 15 mg	(<1), Mild or moderate: 23 (11)				Unspecified ITT: Yes Grp1: 11 (5.5) Grp2: 7 (3.4)	
Hanefeld, 2007[82] RCT	Grp1: Rosiglitazone Fixed Start: 8 mg Grp2: Glibenclamide Varied Start: 2.5 mg, Max: 15 mg D: 12 wks	Coll: NR Timing: Unspecified ITT: Yes Grp1: 3 (1.6) Grp2: Serious: 2 (<1), Mild or moderate: 23 (11)				Def: Unspecified Coll: NR Timing: Unspecified ITT: Yes Grp1: 5 (2.6) Grp2: 7 (3.4)	
Haring, 2014[83] RCT	Grp1:Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Grp2:Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Fixed (10mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptomatic hypoglycemia - presence of typical adrenergic or neuroglycopenic symptoms and signs, regardless of the data for self-monitoring of blood glucose Grp1: (3.51) p 0 Grp2: (19.49) 23 p 0					
Haring, 2014[83] RCT	Grp1:Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose	Def: symptomatic hypoglycemia - presence of typical adrenergic or					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	according to local label)) Grp2:Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Fixed (25mg) ITT:No Mode of AE collection:Active Followup (wks):24	neuroglycopenic symptoms and signs, regardless of the data for self-monitoring of blood glucose Grp1: (6.84) p NS Grp2: (19.49) 23 p 0					
Haring, 2014[83] RCT	Grp1:Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Grp2:Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Fixed (10mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: Severe hypoglycemia, required assistance of another person, according to American Diabetes Association guidelines Grp1: 0 NA p NR Grp2: 0 NA p NR					
Haring, 2014[83] RCT	Grp1:Metformin + placebo Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Grp2:Metformin + empagliflozin Not specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label)) Fixed (25mg) ITT:No Mode of AE collection:Active	Def: Severe hypoglycemia, required assistance of another person, according to American Diabetes Association guidelines Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):24						
Henry, 2012[84] RCT	Grp1:Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2:Dapagliflozin + placebo Fixed (5mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: Severe hypoglycemia, required assistance of another person, according to American Diabetes Association guidelines Grp1: 0 NA p NR Grp2: 0 NA p NR					
Henry, 2012[84] RCT	Grp1:Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2:Dapagliflozin + placebo Fixed (5mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: Severe hypoglycemia, required assistance of another person, according to American Diabetes Association guidelines Grp1: 0 NA p NR Grp2: 0 NA p NR					
Henry, 2012[84] RCT	Grp1:Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: Severe hypoglycemia, required assistance of another person, according to American Diabetes Association guidelines Grp1: 0 NA p NR Grp2: 0 NA p NR					
Henry, 2012[84] RCT	Grp1:Metformin + placebo Titrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg) Grp2:Metformin + dapagliflozin	Def: Severe hypoglycemia, required assistance of another person, according to					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT:No Mode of AE collection:Active Followup (wks):24	American Diabetes Association guidelines Grp1: 0 NA p NR Grp2: 0 NA p NR					
Henry, 2012[84] RCT	Grp1:Dapagliflozin + placebo Fixed (5mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: requiring medical or non-medical assistance Grp1: 283.4Person-years p NR Grp2: 2 283.4 Person-years p NR					
Henry, 2012[84] RCT	Grp1:Dapagliflozin + placebo Fixed (5mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1773.5 mgMax: 2000mg) Fixed (5 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: requiring (nonmedical) assistance of others, requiring medical intervention, or exhibiting markedly depressed level of consciousness, loss of consciousness, or seizure were considered severe Grp1: (2.8) NA p NR Grp2: (1.4) NA p NR					
Henry, 2012[84] RCT	Grp1:Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2:Dapagliflozin + placebo Fixed (10 mg)	Def: severe symptomatic hypogly Grp1: 1 Person-years p NR Grp2: 3 (1) 0.76 Person-years p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:No Mode of AE collection:Active Followup (wks):24						
Henry, 2012[84] RCT	Grp1:Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2:Dapagliflozin + placebo Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptomatic episode requiring external assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <3 mmol/l and prompt recovery after glucose or glucagon administration Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Henry, 2012[84] RCT	Grp1:Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptomatic episode requiring external assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <3 mmol/l and prompt recovery after glucose or glucagon administration Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		NR					
Henry, 2012[84] RCT	Grp1:Metformin + placebo Titrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptomatic episode requiring external assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <3 mmol/l and prompt recovery after glucose or glucagon administration Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Henry, 2012[84] RCT	Grp1:Dapagliflozin + placebo Fixed (10 mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: requiring third-party assistance to administer resuscitative action Grp1: 0 NA p NR Grp2: 0 NA p NR					
Henry, 2012[84] RCT	Grp1:Dapagliflozin + placebo Fixed (10 mg) Grp2:Metformin + dapagliflozin Titrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg) Fixed (10 mg) ITT:No Mode of AE collection:Active	Def: loss of consciousness, seizure, or coma that resolved after treatment with glucagon or glucose, or severe impairment that required third-party					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):24	assistance to resolve the episode and a blood glucose concentration of lower than 3 mmol/L. Grp1: 0 p NR Grp2: 0 p NR					
Hermann, 1994[86] RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Glyburide Varied Start: 3.5 mg, Max: 10.5 mg	Def: Serious Grp1: 8 (21) Grp2: 12 (35)				Def: Nausea + diarrhea + dyspepsia and digestive Grp1: (63) Grp2: (32)	
Hermann, 1994[86] RCT	Grp1: Metformin Varied Start: 1000 mg, Max: 3000 mg Grp2: Metformin + glyburide Varied Start: 500 mg, Max: 3000 mg; Start: 1.75 mg, Max: 14 mg	Def: Mild or moderate Grp1: 8 (21) Grp2: 24 (33)					
Hermans, 2012[87] RCT	Grp1:Metformin Titrated (1500mgMean: mean additional dose (on top of 1500 mg) was 904 mgadded 500mg qd or bid depending on clinical determination) Grp2:Metformin + saxagliptin Fixed (1500 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: loss of consciousness, seizure, or coma that resolved after treatment with glucagon or glucose, or severe impairment that required third-party assistance to resolve the episode and a blood glucose concentration of lower than 3 mmol/L. Grp1: 0 p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Grp2: 0 p NR					
Hong, 2013[195] RCT	Grp1:Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2:Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT:Yes Mode of AE collection:Active Followup (wks):144	Def: loss of consciousness, seizure, or coma that resolved after treatment with glucagon or glucose, or severe impairment that required third-party assistance to resolve the episode and a blood glucose concentration of lower than 3 mmol/L. Grp1: 0 p NR Grp2: 0 p NR					
Hong, 2013[195] RCT	Grp1:Metformin + placebo Titrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) Grp2:Glipizide + placebo Titrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l)) ITT:No Mode of AE collection:Active Followup (wks):144	Def: an event requiring assistance of another Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Hsiao, 2009[215] Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 578 (1.26); ref Grp2: 67 (3.33); HR: 1.30 (CI: 0.89 to 1.89)			
Hsiao, 2009[215] Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 578 (1.26); ref Grp2: 13 (2.66); HR: 1.54 (CI: 0.65 to 3.64)			
Hsiao, 2009[215] Cohort	Grp1: Rosiglitazone NR Grp2: Pioglitazone			Def: ICD-9-CM diagnostic			

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	NR			codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 67 (3.33) Grp2: 13 (2.66)			
Hsiao, 2009[215] Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 67 (3.33); Grp2: 1872 (1.97)			
Hsiao, 2009[215] Cohort	Grp1: Pioglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9-CM diagnostic codes of hospitalization Coll: NR Timing: Unspecified ITT: NA Grp1: 13 (2.66)			

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
				Grp2: 1872 (1.97)			
Jadzinsky, 2009[91] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 week Grp2: Saxagliptin Fixed Mean: 10 mg	Coll: Active Timing: Unspecified ITT: Yes Grp1: Severe: 0 (0) Mild/moderate: 13 (4) Grp2: Severe: 0 (0) Mild/moderate: 5 (1)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 24 (7) Grp2: 10 (3)	
Jadzinsky, 2009[91] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 week Grp2: Metformin + saxagliptin Varied, prespecified dose Start: 500 mg, Max: 1000 mg; Start: 5 mg	Coll: Active Timing: Unspecified ITT: Yes Grp1: Severe: 0 (0) Mild/moderate: 13 (4) Grp2: Severe: 0 (0) Mild/moderate: 11 (3)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 24 (7) Grp2: 22 (7)	
Jadzinsky, 2009[91] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 1000 mg D: 1 week Grp2: Metformin + saxagliptin Varied, prespecified dose Start: 500 mg, Max: 1000 mg; Start: 10 mg	Coll: Active Timing: Unspecified ITT: Yes Grp1: Severe: 0 (0) Mild/moderate: 13 (4) Grp2: Severe: 2 (1) Mild/moderate: 16 (5)				Def: Diarrhea Coll: Active Timing: Unspecified ITT: Yes Grp1: 24 (7) Grp2: 31	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						(10)	
Jain, 2006[92] RCT	Grp1: Pioglitazone Varied, glucose: FPG (69-141 mg/dl) Start: 15 mg, Max: 45 mg, Median: 45 mg Grp2: Glyburide Varied, glucose: FPG: 69-141 mg/dl Start: 5 mg, Max: 15 mg, Median: 10 mg	Def: Mild or moderate Coll: Active Timing: Unspecified ITT: Yes Grp1: 11 (4.4) Grp2: 61 (24.3)			Def: Ankle Coll: Active Timing: No ITT: Yes Grp1: (0) Grp2: (0.8)	Def: diarrhea Coll: active Timing: Unspecified ITT: Yes Grp1: (6) Grp2: (6.4)	Def: stage IV colon ca Coll: active Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 2 (0.8)
Ji, 2015[93] RCT	Grp1: Metformin Titrated (Max: 2000 mg) Grp2: Metformin + linagliptin Titrated (MAX: 1000 mg) Fixed (5mg)	Def: unspecified AE Grp1: 5.797 (1.7) Grp2: 1.788 (0.6)				Def: mild: abd pain Grp1: 21 (6.2) Grp2: 10 (3.4) Def: mild: decreased appetite Grp1: 8 (2.3) Grp2: 3 (1) Def: mild: nausea Grp1: 16 (4.7) Grp2: 13 (4.4) Def: moderate or severe: nausea	Def: acute pancreatitis Grp1: 0 (0) Grp2: 1 (0.3) Def: pancreatic cancer Grp1: NR Grp2: NR

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						Grp1: 8 (2.3) Grp2: 4 (1.3) Def: moderate or severe: decreased appetite Grp1: 3 (0.9) Grp2: 3 (1) Def: moderate or severe: abd pain Grp1: 11 (3.2) Grp2: 7 (2.3) Def: severe or moderate: vomiting Grp1: 1 (0.3) Grp2: 5 (1.7) Def: moderate or severe GI: diarrhea Grp1: 19 (5.6) Grp2: 19	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						(6.4) Def: mild: diarrhea Grp1: 54 (15.8) Grp2: 36 (12.1) Def: mild: vomiting Grp1: 6 (1.8) Grp2: 5 (1.7)	
Jones, 2003[202] RCT	Grp1: Metformin Fixed Max: 2.5 g Grp2: Metformin + rosiglitazone Fixed; Varied, prespecified target Max: 2.5 g; Max: 8 mg	Def: Symptomatic hypoglycemia Grp1: All: (0.4), Obese: (1.7) Grp2: All: (2.1), Obese: (1.9)					
Kadoglou, 2011[95] RCT	Grp1:Metformin Fixed (1700mg daily) Grp2:Metformin + rosiglitazone Fixed (500mg daily) Fixed (4mg daily) ITT:No Mode of AE collection: NR/unclear Followup (wks):24	Def: requiring external assistance due to severely impaired consciousness or behaviour, with capillary or plasma glucose levels <3.0 mmol/l and recovery after glucose or glucagon administration Grp1: 0 NA p NR Grp2: 0 NA p NR					
Kadowaki, 2013[96] RCT	Grp1:Metformin + placebo Fixed (maintained previous dosage40% on 500 mg/day;	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	56% on 750 mg/day; 3% on 1000 mg/day; 1.4% on 1500 mg/day) Grp2:Metformin + sitagliptin Fixed (maintained previous dosage43% on 500 mg/day; 51% on 750 mg/day; 3% on 1000mg/day; 4% on 1500 mg/day) Fixed (50mg qd) ITT:Yes Mode of AE collection:Active Followup (wks):12						
Kahn, 2006[97] RCT	Grp1: Metformin Varied, glucose: <140 mg Start: 500 mg, Max: 2000 mg Grp2: Rosiglitazone Varied, glucose: <140 mg Start: 4 mg, Max: 8 mg	Def: Self reported Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 168 (11.6), Severe: 1 (0.1) Grp2: All: 142 (9.8), Severe: 1 (0.1)		Def: Investigator reported Grp1: 19 (1.3) Grp2: 22 (1.5)		Def: Nausea, vomiting, diarrhea, abdominal discomfort Coll: NR Timing: Unspecified ITT: Yes Grp1: (38.3) Grp2: (23)	
Kahn, 2006[97] RCT	Grp1: Metformin Varied, glucose: <140 mg/dL Start: 500 mg, Max: 2000 mg Grp2: Glyburide Varied, glucose: <140 mg/dL Start: 2.5 mg, Max: 15 mg	Def: Self reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 168 (11.6), Severe: 1 (0.1) Grp2: All: 557 (38.7), Severe: 8 (0.6)		Def: Investigator reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 19 (1.3),		Def: Nausea, vomiting, diarrhea, abdominal discomfort Coll: NR Timing: Unspecified	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
				Serious: 12 (0.8) Grp2: All: 9 (0.6), Serious: 3 (0.2)		ITT: Yes Grp1: (38.3) Grp2: (21.9)	
Kahn, 2006[97] RCT	Grp1: Rosiglitazone Varied, glucose: <140 mg/dl Start: 4 mg, Max: 8 mg Grp2: Glyburide Varied, glucose: <140 mg/dl Start: 2.5 mg, Max: 15 mg	Def: Self reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: Serious events: 1 (0.1), Mild or moderate events: 142 (9.8) Grp2: Serious events: 8 (0.6), Mild or moderate events: 557 (38.7)		Def: Investigator reported events Coll: NR Timing: Unspecified ITT: Yes Grp1: All: 22 (1.5), Serious: 12 (0.8) Grp2: All: 9 (0.6), Serious: 3 (0.2), p: ≤ 0.05		Def: Nausea, vomiting, diarrhea, abdominal discomfort Grp1: (23) Grp2: (21.9)	
Kahn, 2008[220] RCT	Grp1: Metformin Varied, glucose: < 140 Start dose: 500g, Max: 2g Grp2: Rosiglitazone Varied, glucose: < 140 Start dose: 4mg, Max: 8mg				Def: Fractures (NS) Coll: NR Timing: Unspecified ITT: Yes Grp1: 1.2/ 100 patient-years Grp2: 1.86/ 100		

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
					patient-years HR: 1.57 (CI: 1.13 - 2.17), p: 0.0073		
Kahn, 2008[220] RCT	Grp1: Metformin Varied, glucose: < 140 mg/dL Start dose: 500 mg, Max: 2 g Grp2: Glyburide Varied, glucose: < 140 mg/dL Start dose: 2.5 mg, Max: 15 mg				Def: Fractures (NS) Coll: NR Timing: Unspecified ITT: Yes Grp1: 1.2/100 patient-years Grp2: 1.15/100 patient-years		
Kaku, 2009[98] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 750 mg Grp2: Metformin + pioglitazone Varied Start: 500 mg, Max: 750 mg; Start: 15 mg, Max: 30 mg D: NR; 16 wks	Def: Mild or moderate Grp1: 0 (0) Grp2: 1 (1)				Def: abdominal pain and constipation Grp1: (2.3) Grp2: (2.4)	
Kaku, 2011[99] RCT	Grp1:Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2:Liraglutide Titrated (Max: 0.9 mg/d) ITT:No Mode of AE collection:Active	Def: those needing assistance of another individual or resulting in sei zure or loss of consciousness					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):52	Grp1: 15 (3) p NR Grp2: 2 p NR					
Kaku, 2011[99] RCT	Grp1:Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2:Liraglutide Titrated (Max: 0.9 mg/d) ITT:No Mode of AE collection:Active Followup (wks):52	Def: those needing assistance of another individual or resulting in sei zure or loss of consciousness Grp1: 15 (3) p NR Grp2: 3 p NR					
Kaku, 2011[99] RCT	Grp1:Glibenclamide Fixed (1.25 -2.5 mg/d) Grp2:Liraglutide Titrated (Max: 0.9 mg/d) ITT:No Mode of AE collection:Active Followup (wks):52	Def: either any hypoglycemic episode with symptoms consistent with hypoglycemia that led to loss of consciousness or seizure, with prompt recovery in response to glucagon or glucose administration, or documented hypoglycemia [plasma glucose <3.0mmol Grp1: 0 NA p NR Grp2: 0 NA p NR					
Kawai, 2008[231] Non-randomized	Grp1: Metformin NR Start: 500-750mg, Max: 750mg Grp2: Pioglitazone Fixed NR	Def: Mild, moderate and severe Coll: NR Timing: Unspecified ITT: Yes Grp1: 0 (0) Grp2: 0 (0)					
Kawai, 2008[231]	Grp1: Metformin	Def: Mild, moderate					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Non-randomized	NR Start: 500-750 mg, Max: 750 mg Grp2: Metformin + pioglitazone NR; Fixed Start: 500-750 mg, Max: 750 mg; NR	and severe Coll: NR Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 0 (0)					
Kim, 2014[103] RCT	Grp1:Metformin Titrated (Max: 2500 mg/day) Grp2:Metformin + glimepiride Titrated (Max: 2000 mg/day) Fixed (1-8 mg/day) ITT:No Mode of AE collection: NR/unclear Followup (wks):26	Def: Any episode with symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose lower than 3.0 mmol/L necessitating the assistance of another person because of sev Grp1: 1 NA p NR Grp2: 1 NA p NR					
Kvapil, 2006[105] RCT	Grp1: Metformin + glibenclamide Fixed; Varied Mean: 1660 mg; Start: 1.75 mg, Max: 10.5 mg, Mean: 6.58 mg Grp2: Metformin + aspart 70/30 Fixed; Varied, glucose: 5 - 8 mmol/L Mean: 1660 mg; Start: 0.2 U/kg bid, Mean: 0.30 U/kg bid	Coll: NR Timing: Unspecified ITT: Yes Grp1: Severe: 0, Mild or moderate: 9 (8) Grp2: Severe: 0, Mild or moderate: 13 (12)					
Lavalle-Gonzalez, 2013[106]	Grp1:Metformin + placebo Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to	Def: de fi ned as a hypoglycemic episode in which the					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	tolerate higher dose])) Grp2:Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR Mode of AE collection:Active Followup (wks):52	patient had a documented blood glucose <3.0 mmol/L and lost con- sciousness or required the assistance of another person because of severe impair- ment in consciousness or behavior) Grp1: 0 Persons p Grp2: 0 Persons p					
Lavalle-Gonzalez, 2013[106] RCT	Grp1:Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2:Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: symptoms of blurry vision, confusion, coma, seizure requiring assistance of another person Grp1: NA p NR Grp2: 0 NA p NR					
Lavalle-Gonzalez, 2013[106] RCT	Grp1:Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2:Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR Mode of AE collection:Active	Def: Unspecified AE Grp1: p Grp2: 0 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):52						
Lavalle-Gonzalez, 2013[106] RCT	Grp1:Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2:Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 12 NA p NR Grp2: 1 NA p NR					
Lavalle-Gonzalez, 2013[106] RCT	Grp1:Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2:Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 0 (0) Persons p 0.319 Grp2: 1 Persons p					
Lavalle-Gonzalez, 2013[106] RCT	Grp1:Metformin + placebo Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Grp2:Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: required third-party assistance Grp1: NA p NR NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Lavalle-Gonzalez, 2013[106] RCT	Grp1:Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2:Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: required third-party assistance Grp1: NA p NR Grp2: 1 NA p NR					
Lavalle-Gonzalez, 2013[106] RCT	Grp1:Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2:Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: severe events (>/= 1 major event or recurring minor events) Grp1: 7 NA p NR Grp2: 0 NA p NR					
Lavalle-Gonzalez, 2013[106] RCT	Grp1:Metformin + sitagliptin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2:Metformin + canagliflozin Fixed ((ГёÑ2,000 mg/day [or ГёÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) ITT: NR	Def: requiring medical assistance Grp1: 4 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):52						
Lavalle-Gonzalez, 2013[106] RCT	Grp1:Metformin + sitagliptin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (100mg) Grp2:Metformin + canagliflozin Fixed ((ГëÑ2,000 mg/day [or ГëÑ1,500 mg/day if unable to tolerate higher dose])) Fixed (300mg) ITT: NR Mode of AE collection:Active Followup (wks):52	Def: symptomatic episodes requiring external assistance, with blood glucose level <63 mg/dL [<3.5 mmol/L] and prompt recovery [start and stop of event on same date] Grp1: NA p NR Grp2: 0 NA p NR					
Lee, 2013[223] Prospetive cohort	Grp1:Metformin + pioglitazone Not specified (Mean: 1000mg) Fixed (15mg) Grp2:Metformin + sitagliptin Not specified (Mean: 1000mg) Fixed (150mg) ITT:Not applicable (e.g., cohort) Mode of AE collection:Passive Followup (wks):	Def: number of events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Lee, 2013[223] Prospetive cohort	Grp1:Metformin + pioglitazone Not specified (Mean: 1000mg) Fixed (15mg) Grp2:Albiglutide + su Not specified (Mean: 1000mg) Not specified (Max: 30-60mg for gliclazide, 2.5-4mg for glimeperide) ITT:Not applicable (e.g., cohort) Mode of AE collection:Passive Followup (wks):	Def: number of events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 1 NA p NR Grp2: 0 NA p NR					
Lee, 2013[223]	Grp1:Metformin + sitagliptin	Def: number of					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Prospetive cohort	Not specified (Mean: 1000mg) Fixed (150mg) Grp2:Albiglutide + su Not specified (Mean: 1000mg) Not specified (Max: 30-60mg for gliclazide, 2.5-4mg for glimeperide) ITT:Not applicable (e.g., cohort) Mode of AE collection:Passive Followup (wks):	events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Leiter 2005[108] RCT	Grp1: Metformin Varied, glucose: <7.0 mmol/L Start: 1500 mg, Max: 2500 mg D: 8 wks Grp2: Rosiglitazone Varied, glucose: <7.0 mmol/L Start: 4 mg, Max: 8 mg D: 8 wks			Grp1: 0 (0) Grp2: 3 (1)			
List, 2009[109] RCT	Grp1:Metformin Titrated (Max: 1500 mg/d) Grp2:Dapagliflozin Fixed (5mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Def: number of events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
List, 2009[109] RCT	Grp1:Metformin Titrated (Max: 1500 mg/d) Grp2:Dapagliflozin Fixed (10 mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Def: number of events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 1 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Grp2: 0 NA p NR					
Madsbad, 2004[110] RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.75 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					
Madsbad, 2004[110] RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.60 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 1 (3)					
Madsbad, 2004[110] RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.45 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					
Madsbad, 2004[110] RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.225 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					
Madsbad, 2004[110] RCT	Grp1: Glimepiride Varied, FPG < 7 mmol/L Start: 1 mg; Max: 4 mg D: 4 wks Grp2: Liraglutide Fixed Mean: 0.045 mg	Def: Glucose < 2.8 mmol/L Coll: Active Timing: Specified ITT: Yes Grp1: 4 (15) Grp2: 0 (0)					
Maffioli,	Grp1:Metformin + pioglitazone	Def: number of					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
2013[111] RCT	Fixed (2550 mg) Fixed (30 mg) Grp2:Metformin + glibenclamide Fixed (2550 mg) Fixed (10 mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):24	events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 1 NA p NR Grp2: 0 NA p NR					
Malone, 2003[112] RCT	Grp1: Metformin + glibenclamide Varied, glucose: fasting and pre-meal <7mmol.L, 2-hour post-prandial <10mmol/L Max: 2550 mg, Mean: 1968 mg; Mean: 14.2 mg D: 4 wks Grp2: Metformin + lispro 75/25 fasting and pre-meal <7mmol.L, 2-hour post-prandial <10mmol/L Max: 2550 mg; Mean: 0.19U/kg in am and 0.14 U/kg in evening D: 4 wks	Def: Symptomatic or BG <3.5mmol/l Timing: Unspecified ITT: NR Grp1: (1) Grp2: (1.3)					
Malone, 2004[204] RCT	Grp1: Metformin + glargine Fixed; Varied, glucose: 90 – 126 mg/dL Start: 1500 mg, Max: 2550 mg; Mean: 0.57 U/kg qd Grp2: Metformin + lispro 75/25 Varied, glucose: 90 – 126 mg/dL Start: 1500 mg, Max: 2550 mg; Mean: 0.62 U/kg bid	Def: Coll: Active Timing: Specified ITT: Yes Grp1: Severe: 0 (0), Mild or moderate: 40 (40) Grp2: Severe: 0 (0), Mild or moderate: 57 (57)		Coll: Active Timing: Specified ITT: Yes Grp1: 0 (0) Grp2: 1 (1)			
Malone, 2005[205] RCT	Grp1: Metformin + lispro 75/25 Varied, pre-meal glucose 90-126 mg/dL 2-hr PPG 144-180 mg/dL	Def: Overall Coll: Active Timing: Specified ITT: NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 1500 mg; Max: 2550 mg; Mean: 2146 mg; Mean: 0.42 U/kg bid D: 4 wks; 16 wks Grp2: Metformin + glargine Varied, glucose 90-126 mg/dL Start: 1500 mg; Max: 2550 mg; Mean: 2146 mg; Mean: 0.36 U/kg qd D: 4 wks; 16 wks	Grp1: 0.61 episodes/ patient/30 days Grp2: 0.44 episodes/ patient/30 days					
Marre, 2002[113] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Glibenclamide Varied Start: 5 mg, Max: 20 mg	Def: Symptoms or labs Grp1: Serious: 1 (1.0), Mild or moderate: 0 (0) Grp2: Serious: 1 (1.0), Mild or moderate: 7 (7)					
Marre, 2002[113] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Def: Symptoms or labs Grp1: Serious: 1 (1.0), Mild or moderate: 0 Grp2: Serious: 0, Mild or moderate: 11 (10.9)				Def: Not specified Grp1: (14.4) Grp2: (6.9)	
Marre, 2002[113] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 2000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000 mg; Start: 2.5 mg, Max: 10 mg	Def: Symptoms or labs Grp1: Serious: 1 (1.0), Mild or moderate: 0 Grp2: Serious: 2 (1.9), Mild or moderate: 12 (11.4)					
Moon, 2014[114] RCT	Grp1:Metformin + glimepiride Fixed (Mean: 1426.5mgdose the same as met dose prior to	Def: number of events requiring the assistance of					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	study, discontinued if FBG was controlled at target level with glimepiride<=0.25mg/day) Titrated (Mean: 4.3Max: 8mgstarting 1mg/day, increased to 2mg/day at second week, up to 8mg/day at week 3,5,7 with target FBG of 90-130mg/dl as per the investigator's discretion) Grp2:Metformin + insulin glargine Fixed (Mean: 1365.1mgdose the same as met dose prior to study) Titrated (Mean: 22.8 unitsstarting at 0.2U/kg of body weight, titrated every 3 days by 2IU with target FBG of 90-130mg/dl as per the investigator's discretion; discontinued if FBG was controlled at target level with glargine<=8IU) ITT:No Mode of AE collection:Active Followup (wks):48	another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Moon, 2014[114] RCT	Grp1:Metformin + glimepiride Fixed (Mean: 1426.5mgdose the same as met dose prior to study, discontinued if FBG was controlled at target level with glimepiride<=0.25mg/day) Titrated (Mean: 4.3Max: 8mgstarting 1mg/day, increased to 2mg/day at second week, up to 8mg/day at week 3,5,7 with target FBG of 90-130mg/dl as	Def: number of events requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	per the investigator's discretion) Grp2:Metformin + insulin glargine Fixed (Mean: 1365.1mgdose the same as met dose prior to study) Titrated (Mean: 22.8 unitsstarting at 0.2U/kg of body weight, titrated every 3 days by 2IU with target FBG of 90-130mg/dl as per the investigator's discretion; discontinued if FBG was controlled at target level with glargine<=8IU) ITT:No Mode of AE collection:Active Followup (wks):48						
Nauck, 2007[118] RCT	Grp1: Metformin + glipizide Varied; Varied, glucose: <6.1 mmol/l NR; Start: 5 mg, Max: 20 mg D: NR, 18 wks Grp2: Metformin + sitagliptin Varied; Fixed NR	Def: Severe Coll: Active Timing: Specified ITT: Yes Grp1: 7 (1) Grp2: 1 (<1)				Def: Diarrhea, abdominal pains, nausea, vomiting Coll: Active Timing: Specified ITT: Yes Grp1: 69 (12) Grp2: 70 (12)	
Nauck, 2009[119] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose)	Def: required assistance of another person to actively administer					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Nauck, 2009[119] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2:Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Nauck, 2009[119] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2:Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: requring assistance Grp1: 0 p Grp2: 0 p					
Nauck, 2009[119] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2:Metformin + alogliptin	Def: requring assistance Grp1: 0 p Grp2: 0 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):26						
Nauck, 2009[119] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2:Metformin + alogliptin Fixed (Mean: 1846mg>=1500mg or maximum tolerated dose) Fixed (25mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: i.e., symptomatic episode requiring third-party assistance because of severe impairment in consciousness or behaviour, with capillary or plasma glucose < 3.00 mmol, and prompt recovery after glucose or glucagon administration). Grp1: 0 p Grp2: 0 p					
Nauck, 2009[119] RCT	Grp1:Metformin + placebo Fixed (Mean: 1868mg>=1500mg or maximum tolerated dose) Grp2:Metformin + alogliptin Fixed (Mean: 1837mg>=1500mg or maximum tolerated dose) Fixed (12.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: i.e., symptomatic episode requiring third-party assistance because of severe impairment in consciousness or behaviour, with capillary or plasma glucose < 3.00 mmol â□„ l, and prompt					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		recovery after glucose or glucagon administration). Grp1: 0 p Grp2: 0 p					
Nauck, 2011[120] RCT	Grp1:Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2:Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: i.e., symptomatic episode requiring third-party assistance because of severe impairment in consciousness or behaviour, with capillary or plasma glucose < 3.00 mmol â□„ l, and prompt recovery after glucose or glucagon administration). Grp1: 0 p Grp2: 0 p					
Nauck, 2011[120] RCT	Grp1:Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2:Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol â□„ l, and prompt recovery after glucose or glucagon					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		administration Grp1: 0 p Grp2: 0 p					
Nauck, 2011[120] RCT	Grp1:Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2:Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol â□„ l, and prompt recovery after glucose or glucagon administration Grp1: 0 p Grp2: 0 p					
Nauck, 2011[120] RCT	Grp1:Metformin + glipizide Fixed (1500 - 2500 mg) Titrated (Mean: 16.4 mgMax: 20 mg) Grp2:Metformin + dapagliflozin Fixed (1500 - 2500 mg) Titrated (Mean: 9.2 mgMax: 10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):104	Def: symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol â□„ l, and prompt recovery after glucose or glucagon administration Grp1: 0 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Grp2: 0 p					
Nauck, 2014[121] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: hypoglycemic attack: severe hypoglycemia in which the subject required assistance and/or a plasma glucose level <56 mg/dl [3.1mmol/l] Grp1: 3 NA p 0.651 Grp2: 4 NA p					
Nauck, 2014[121] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic attack: severe hypoglycemia in which the subject required assistance and/or a plasma glucose level <56 mg/dl [3.1mmol/l] - this is in group excluding those needing hyperglycemic rescue with insulin Grp1: 0 NA p 0.08 Grp2: 3 NA p					
Nauck, 2014[121] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: hypoglicemia requiring 3rd part assistance Grp1: 0 p Grp2: 0 0 p					
Nauck, 2014[121] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide	Def: Unspecified AE Grp1: 0 (0) p Grp2: 0 (0) 0 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52						
Nauck, 2014[121] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: requring assistance Grp1: Persons p Grp2: 1 Persons p					
Nauck, 2014[121] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: requring assistance Grp1: Persons p Grp2: 1 Persons p					
Nauck, 2014[121] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: requring assistance Grp1: Persons p Persons p					
Nauck, 2014[121] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: requring assistance Grp1: 1 Persons p Grp2: 1 Persons p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Nauck, 2014[121] RCT	Grp1:Metformin + placebo Fixed (>=1500 mg/day) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: requring assistance Grp1: 1 Persons p Persons p					
Nauck, 2014[121] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: A major hypoglycemic event was defined as blood glucose â‰¤60 mg/dL accompanied by neurological symptoms consistent with hypoglycemia or an episode requiring intervention with intravenous glucose. Grp1: NA p NR Grp2: 0 NA p NR					
Nauck, 2014[121] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: A major hypoglycemic event was defined as blood glucose â‰¤60 mg/dL accompanied by neurological symptoms consistent with hypoglycemia or an episode requiring intervention with intravenous glucose. Grp1: NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Grp2: 0 NA p NR					
Nauck, 2014[121] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: A major hypoglycemic event was defined as blood glucose â‰¤60 mg/dL accompanied by neurological symptoms consistent with hypoglycemia or an episode requiring intervention with intravenous glucose. Grp1: NA p NR Grp2: 0 NA p NR					
Nauck, 2014[121] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: severe hypoglycemia: any episode requiring the assistance of another party accompanied by plasma glucose value < 2.0mmol/l or symptom resolved after oral or intravenous glucose or intravenous glucagon ingestion Grp1: 0 NA p Grp2: 0 NA p N/A					
Nauck, 2014[121] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (0.75 mg/week)	Def: any episode that requires assistance associated with a documented blood glucose < 60mg/dl					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:Yes Mode of AE collection:Active Followup (wks):52	Grp1: 0 NA p NR Grp2: 0 NA p NR					
Nauck, 2014[121] RCT	Grp1:Metformin + sitagliptin Fixed (>=1500 mg/day) Fixed (100 mg) Grp2:Metformin + dulaglutide Fixed (>=1500 mg/day) Fixed (1.5 mg/week) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: any episode that requires assistance associated with a documented blood glucose < 60mg/dl Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pantalone, 2009[208] Cohort	Grp1: Metformin NR Grp2: Rosiglitazone NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: ref Grp2: HR: 1.16 (CI: 0.78 to 1.73)			
Pantalone, 2009[208] Cohort	Grp1: Metformin NR Grp2: Pioglitazone NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: ref Grp2: HR: 1.38 (CI: 1.00 to 1.90)			
Pantalone, 2009[208] Cohort	Grp1: Metformin NR Grp2: Sulfonylurea NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA			

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
				Grp1: HR: 0.76 (CI: 0.64 to 0.91) Grp2: ref			
Pantalone, 2009[208] Cohort	Grp1: Rosiglitazone NR Grp2: Pioglitazone NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: ref Grp2: HR: 1.19 (CI: 0.74to 1.91)			
Pantalone, 2009[208] Cohort	Grp1: Rosiglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: HR: 0.88 (CI: 0.60 to 1.31) Grp2: ref			
Pantalone, 2009[208] Cohort	Grp1: Pioglitazone NR Grp2: Sulfonylurea NR			Def: ICD-9 codes Coll: NR Timing: NA ITT: NA Grp1: HR: 1.05 (95% CI 0.77 to 1.43) Grp2: ref			
Pavo, 2003[123] RCT	Grp1: Metformin Varied, glucose: < 126 mg/dl					Def: Diarrhea	Def: Cholecysti

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 850 mg, Max: 2550 mg, Mean: 2292 mg D: 8 wks Grp2: Pioglitazone Varied, glucose: < 126 mg/dl Start: 35 mg, Max: 45 mg, Mean: 41.5 mg D: 8 wks					Grp1: (16) Grp2: (3)	tis Coll: Active Timing: Unspecified ITT: NR Grp1: 0 (0) Grp2: 1 (1)
Perez, 2009[125] RCT	Grp1: Metformin Fixed Mean: 850 mg Grp2: Pioglitazone Fixed				Def: Wrist fractures Coll: Active Timing: Specified ITT: NR Grp1: 1 (<1) Grp2: 0 (0)	Def: Diarrhea Coll: Active Timing: Specified ITT: NR Grp1: (15.3) Grp2: (2.6)	
Perez, 2009[125] RCT	Grp1: Metformin Fixed Mean: 850 mg Grp2: Metformin + pioglitazone Fixed				Def: Wrist fractures Coll: Active Timing: Specified ITT: NR Grp1: 1 (<1) Grp2: 1 (<1)	Def: Diarrhea Coll: Active Timing: Specified ITT: NR Grp1: (15.3) Grp2: (9)	
Pfutzner, 2011[128]	Grp1:Metformin + pioglitazone Fixed (1700 mg/d)	Def: discontinued study due to					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Fixed (30 mg/d) Grp2:Metformin + glimepiride Fixed (1700 mg/d) Fixed (2mg/d) ITT:No Mode of AE collection: NR/unclear Followup (wks):24	hypoglycemia Grp1: 7 (1.7) 408Persons p NR Grp2: 0 (0) 406 Persons p NR					
Pfutzner, 2011[129] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Saxagliptin + placebo Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required external assistance because of severely impaired consciousness or behavior, with capillary or plasma glucose levels <3.0 mmol/L and recovery after glucose or glucagon administration Grp1: 3 (0.7) 408Persons p NR Grp2: 0 (0) 406 Persons p NR					
Pfutzner, 2011[129] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Saxagliptin + placebo Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: Persons p NR Grp2: 0 315 Persons p NR					
Pfutzner, 2011[129] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg)	Def: required the assistance of another person to actively administer					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	therapy Grp1: 0 177Persons p NR Grp2: 0 315 Persons p NR					
Pfutzner, 2011[129] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: Persons p NR Grp2: 0 302 Persons p NR					
Pfutzner, 2011[129] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: Persons p NR Grp2: 0 304 Persons p NR					
Pfutzner, 2011[129] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: 0 177Persons p NR Grp2: 0 302 Persons p NR					
Pfutzner, 2011[129] RCT	Grp1:Saxagliptin + placebo Fixed (10 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg)	Def: required the assistance of another person to actively administer therapy					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:Yes Mode of AE collection:Active Followup (wks):76	Grp1: 0 177Persons p NR Grp2: 0 304 Persons p NR					
Pfutzner, 2011[129] RCT	Grp1:Saxagliptin + placebo Fixed (10 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: 0 315Persons p NR Grp2: 0 302 Persons p NR					
Pfutzner, 2011[129] RCT	Grp1:Saxagliptin + placebo Fixed (10 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: 0 315Persons p NR Grp2: 0 304 Persons p NR					
Pfutzner, 2011[129] RCT	Grp1:Saxagliptin + placebo Fixed (10 mg) Grp2:Metformin + saxagliptin Titrated (Max: 2000 mg) Fixed (10 mg) ITT:Yes Mode of AE collection:Active Followup (wks):76	Def: required the assistance of another person to actively administer therapy Grp1: 0 315Persons p NR Grp2: 0 302 Persons p NR					
Pratley, 2010[130] RCT	Grp1: Metformin + sitagliptin Varied, HbA1c : 7.5% - 10% NS; Max: 100 mg Grp2: Metformin + liraglutide Varied, HbA1c: 7.5% - 10% NS; Start: 0.6 mg Max: 1.2 mg					Def: GI events Coll: NR Timing: Unspecified	Def: Neoplasm Coll: NR Timing: Unspecified

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						ITT: No Grp1: 4 (2) Grp2: 3 (1)	ITT: No Grp1: 1 (<1) Grp2: 0 (0) Def: Pancreatitis Grp1: 0 (0) Grp2: 0 (0)
Pratley, 2010[130] RCT	Grp1: Metformin + sitagliptin Varied, HbA1c : 7.5% - 10% NS; Max: 100 mg Grp2: Metformin + liraglutide Varied, HbA1c: 7.5% - 10% NS; Start: 0.6 mg Max: 1.8 mg					Def: GI events Coll: NR Timing: Unspecified ITT: No Grp1: 4 (2) Grp2: 3 (1)	Def: Neoplasm Coll: NR Timing: Unspecified ITT: No Grp1: 1 (<1) Grp2: 1 (<1) Def: Pancreatitis Grp1: 0 (0) Grp2: 0 (0)
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No	Def: required the assistance of another person to actively administer therapy					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):26	Grp1: 0 315Persons p NR Grp2: 0 304 Persons p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (1000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (2000 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):26						
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + alogliptin	Def: hypoglycemic episodes - blood glucose<70mg/dl,					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (1000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: hypoglycemic episodes - blood glucose<70mg/dl, requiring assistance from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: requiring assistance or seizure or LOC Grp1: 0 p Grp2: 0 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (1000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: requiring assistance or seizure or LOC Grp1: 0 p Grp2: 0 p					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: required medical or non-medical assistance or exhibited marked severity (markedly depressed level of consciousness, loss of consciousness, or seizure) Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin Fixed (2000 mg) Grp2:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):26	Def: event requiring assistance Grp1: NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: event requiring assistance Grp1: NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin + alogliptin Fixed (2000 mg)	Def: any episode requiring assistance					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	from another person Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin + alogliptin Fixed (1000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active Followup (wks):26	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Pratley, 2014[131] RCT	Grp1:Metformin + alogliptin Fixed (2000 mg) Fixed (25 mg) Grp2: + alogliptin Fixed (25mg qd) ITT:No Mode of AE collection:Active	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):26						
Qiu, 2014[132] RCT	Grp1:Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2:Metformin + canagliflozin Fixed (Mean: 2137mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (50mg BID) ITT:Yes Mode of AE collection:Active Followup (wks):18	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Qiu, 2014[132] RCT	Grp1:Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2:Metformin + canagliflozin Fixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (150mg BID) ITT:Yes Mode of AE collection:Active Followup (wks):18	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Qiu, 2014[132] RCT	Grp1:Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	dose) for >=8 wks prior to screening) Grp2:Metformin + canagliflozin Fixed (Mean: 2137mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (50mg BID) ITT:Yes Mode of AE collection:Active Followup (wks):18						
Qiu, 2014[132] RCT	Grp1:Metformin + placebo Fixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening) Grp2:Metformin + canagliflozin Fixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening) Fixed (150mg BID) ITT:Yes Mode of AE collection:Active Followup (wks):18	Def: assistance of another person was required to actively administer carbohydrate, glucagon or other resuscitative actions Grp1: 0 NA p NR Grp2: 0 NA p NR					
Raskin, 2007[134] RCT	Grp1: Metformin + glargine Fixed; Varied, premeal glucose: 4.4 - 6.1mmol/L NR; Start: 12 U/kg QD, Mean: 0.57 IU/kg QD Grp2: Metformin + aspart 70/30 Fixed; Varied, premeal glucose: 4.4 - 6.1mmol/L NR; Start: 12 IU/kg BID, Mean: 0.91 IU/kg	Def: mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 11 (14) Grp2: 33 (42)					
Raz, 2008[188]	Grp1: Metformin	Def: Mild or			Def: Limb	Def:	Def:

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Fixed Start: ≥1500 mg Grp2: Metformin + sitagliptin Fixed Start: ≥ 1500 mg; Start: 100 mg	moderate Coll: NR Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 1 (1)			fracture Coll: NR Timing: Unspecified ITT: No Grp1: 1 (1) Grp2: 0 (0)	abdominal pain, nausea, vomiting, or diarrhea Coll: NR Timing: Unspecified ITT: No Grp1: (7.4) Grp2: (10.4)	Neoplasms Coll: NR Timing: Unspecified ITT: No Grp1: 3 (3) Grp2: 0 (0)
Reasner, 2011[135] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):44	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p Grp2: 0 Persons p					
Reasner, 2011[135] RCT	Grp1:Metformin Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg)	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:Yes Mode of AE collection:Active Followup (wks):44	after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p Grp2: 0 Persons p					
Ridderstrale, 2014[136] RCT	Grp1:Metformin + glimepiride Fixed (Mean: 2.71 mg/day (mean max titrated dose of glimep(ГёÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Titrated (Max: 4mg) Grp2:Metformin + empagliflozin Fixed ((ГёÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label) Fixed (25mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p Grp2: 0 Persons p					
Robbins, 2007[138] RCT	Grp1: Metformin + glargine Fixed; Varied, glucose: <6.7 mmol/l Start: 500 mg bid, Max: 1000 mg bid, Mean: 1636 mg; Mean: 0.6 U/kg QD Grp2: Metformin + insulin lispro 50/50 Fixed; Varied, glucose: <6.7	Def: Coll: Active Timing: Specified ITT: Yes Grp1: Severe: 2 (1), Mild or moderate: 75 (47) Grp2: Severe: 3 (2),				Def: Diarrhea Coll: Active Timing: Specified ITT: Yes Grp1:	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	mmol/l Start: 500 mg bid, Max: 1000 mg bid, Mean: 1641 mg; Mean: 0.7 U/kg tid	Mild or moderate: 79 (50)				(5.7) Grp2: (6.4)	
Roden, 2013[139] RCT	Grp1:Sitagliptin Fixed (100 mg) Grp2:Empagliflozin Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p Grp2: 0 Persons p					
Roden, 2013[139] RCT	Grp1:Sitagliptin Fixed (100 mg) Grp2:Empagliflozin Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Grp2: 0 Persons p					
Roden, 2013[139] RCT	Grp1:Sitagliptin Fixed (100 mg) Grp2:Empagliflozin Fixed (10 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in conscious Grp1: 0 Persons p Grp2: 0 Persons p					
Roden, 2013[139] RCT	Grp1:Sitagliptin Fixed (100 mg) Grp2:Empagliflozin Fixed (25 mg) ITT:No Mode of AE collection:Active Followup (wks):24	Def: plasma glucose concentration<=3.9 mmol/l, requiring assistance Grp1: 0 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2006[140] RCT	Grp1: Metformin Varied, mean daily glucose ≤ 6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Rosiglitazone Varied, mean daily glucose ≤ 6.1 mmol/l Start: 4 mg, Max: 8 mg, Mean: 7.7 mg D: 32 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 14 (9) Grp2: 13 (8)				Def: Diarrhea, nausea, vomiting, dyspepsia Coll: Active Timing: Specified ITT: Yes Grp1: (51) Grp2: (35)	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Rosenstock, 2006[140] RCT	Grp1: Metformin Varied, mean daily glucose ≤6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1847 mg D: 32 wks Grp2: Metformin + rosiglitazone Varied, mean daily glucose ≤6.1 mmol/l Start: 500 mg, Max: 2000 mg, Mean: 1799 mg; Start: 2 mg, Max: 8 mg, Mean: 7.2 mg D: 32 wks	Def: Self reported mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 14 (9) Grp2: 19 (12)				Def: Diarrhea, nausea, vomiting Dyspepsia Coll: Active Timing: Specified ITT: Yes Grp1: (51) Grp2: (47)	
Rosenstock, 2010[141] RCT	Grp1:Pioglitazone + placebo Fixed (30mg qd) Grp2:Alogliptin + placebo Fixed (25mg qd) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: hypoglycemia requiring help from a third party to actively administer therapy Grp1: 0 Persons p NR Grp2: 0 Persons p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: hypoglycemia requiring help from a third party to actively administer therapy Grp1: 0 Persons p NR Grp2: 0 Persons p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Rosenstock, 2012[142] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: Unspecified AE Grp1: 0 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1904 mg/day) Fixed (200 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 2 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 1 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1904 mg/day) Fixed (200 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + placebo Fixed (Mean: 1919 mg/day) Grp2:Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 2 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2:Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day)	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:Yes Mode of AE collection:Active Followup (wks):12	of consciousness or seizure) Grp1: 2 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2:Metformin + canagliflozin Fixed (Mean: 1904 mg/day) Fixed (200 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 1 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2:Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 1 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2:Metformin + canagliflozin Fixed (Mean: 1903 mg/day) Fixed (100 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required assistance or exhibited marked severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 0 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg)	Def: required assistance or exhibited marked					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + canagliflozin Fixed (Mean: 1904 mg/day) Fixed (200 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	severity (i.e., depressed level of consciousness, loss of consciousness or seizure) Grp1: 0 NA p NR Grp2: 0 NA p NR					
Rosenstock, 2012[142] RCT	Grp1:Metformin + sitagliptin Fixed (Mean: 1885 mg/day) Fixed (100 mg) Grp2:Metformin + canagliflozin Fixed (Mean: 1874 mg/day) Fixed (300 mg/day) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: required third-party assistance Grp1: 2 Persons p NR Grp2: 0 Persons p NR					
Rosenstock, 2013[144] RCT	Grp1:Metformin + placebo Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Grp2:Metformin + sitagliptin Not specified (prestud dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (100mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Def: required third-party assistance Grp1: 2 Persons p NR Grp2: 0 Persons p NR					
Rosenstock, 2013[144] RCT	Grp1:Metformin + placebo Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Grp2:Metformin + empagliflozin Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose)	Def: required third-party assistance Grp1: 2 Persons p NR Grp2: 0 Persons p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (10mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12						
Rosenstock, 2013[144] RCT	Grp1:Metformin + placebo Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Grp2:Metformin + empagliflozin Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (25mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Def: requiring assistance Grp1: 0 Persons p NR Grp2: 0 Persons p NR					
Rosenstock, 2013[144] RCT	Grp1:Metformin + sitagliptin Not specified (prestud dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (100mg) Grp2:Metformin + empagliflozin Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (10mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	Def: patients with hypoglycemia and need someone to help or to the hospital for treatment Grp1: 0 NA p Grp2: 0 NA p					
Rosenstock, 2013[144] RCT	Grp1:Metformin + sitagliptin Not specified (prestud dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (100mg)	Def: Asymptomatic hypoglycemia, no symptoms but plasma glucose concentration <=					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + empagliflozin Not specified (prestudy dose: ГёÑ1500 mg/day or maximum tolerated dose) Fixed (25mg) ITT:Yes Mode of AE collection: NR/unclear Followup (wks):12	3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1) NA p NR Grp2: (1) NA p NR					
Rosenstock, 2015[145]	Grp1: Metformin + saxagliptin + placebo Not specified (1500-2000 mg/d) Fixed 5mg/d Grp2: Metformin + dapagliflozin + placebo Not specified (1500-2000 mg/d) Fixed 10 mg/d	Def: total Grp1: 0(NR) Grp2: 0(NR) Def: severe Grp1: 1(0.6) Grp2: 1(0.6)			Def: non-hip fracture Grp1: 2(1) Grp2: 1(0.6)		Def: Impaired renal function – GFR decrease Grp1: 1(0.6) Grp2: 0(0) Def: UTI Grp1: 9(5) Grp2: 7(5) Def: genital or mycotic infections Grp1: 1(0.6) Grp2: 10(6) Def: Pancreatitis Grp1: 0(NR) Grp2: 0(NR)
Ross, 2012[146]	Grp1:Metformin + placebo	Def: Documented					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2:Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT:Yes Mode of AE collection:Active Followup (wks):12	symptomatic hypoglycemia, typical symptoms accompanied by a plasma glucose concentration of <=3.9mmol/l, according to American Diabetes Association guidelines Grp1: (4) NA p NR Grp2: (17.9) NA p NR					
Ross, 2012[146] RCT	Grp1:Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2:Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg) ITT:Yes Mode of AE collection:Active Followup (wks):12	Def: Asymptomatic hypoglycemia, no symptoms but plasma glucose concentration <= 3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1) NA p NR Grp2: (1.3) NA p NR					
Ross, 2012[146] RCT	Grp1:Metformin + placebo Fixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose) Grp2:Metformin + linagliptin + placebo Fixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose) Fixed (5mg)	Def: Documented symptomatic hypoglycemia, typical symptoms accompanied by a plasma glucose concentration of <=3.9mmol/l, according to American Diabetes					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:Yes Mode of AE collection:Active Followup (wks):12	Association guidelines Grp1: (4) NA p NR Grp2: (1.7) NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Asymptomatic hypoglycemia, no symptoms but plasma glucose concentration <= 3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1) NA p NR Grp2: (1.3) NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Documented symptomatic hypoglycemia, typical symptoms accompanied by a plasma glucose concentration of <=3.9mmol/l, according to American Diabetes Association guidelines Grp1: (4) NA p NR Grp2: (3) NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg)	Def: Asymptomatic hypoglycemia, no symptoms but plasma glucose					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) ITT:Yes Mode of AE collection:Active Followup (wks):26	concentration <= 3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1) NA p NR Grp2: (1.3) NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Documented symptomatic hypoglycemia, typical symptoms accompanied by a plasma glucose concentration of <=3.9mmol/l, according to American Diabetes Association guidelines Grp1: (17.9) NA p NR Grp2: (1.7) NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Asymptomatic hypoglycemia, no symptoms but plasma glucose concentration <= 3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1) NA p NR Grp2: (1.3) NA p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		NR					
Russell-Jones, 2012[147] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Documented symptomatic hypoglycemia, typical symptoms accompanied by a plasma glucose concentration of <=3.9mmol/l, according to American Diabetes Association guidelines Grp1: (17.9) NA p NR Grp2: (3) NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: Asymptomatic hypoglycemia, no symptoms but plasma glucose concentration <= 3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1.3) NA p NR Grp2: (1.3) NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Exenatide + placebo Fixed (2.0 mg subcut	Def: Documented symptomatic hypoglycemia, typical symptoms accompanied by a plasma glucose					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	concentration of <=3.9mmol/l, according to American Diabetes Association guidelines Grp1: (1.7) NA p NR Grp2: (3) NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Metformin + placebo Titrated (Max: 2500 mg based on glycemic controltarget 2000 mg) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: plasma glucose <=3.9mmol/l(70mg/dl) and/or symptoms of hypoglycemia Grp1: (7.8) NA p NR Grp2: (2.2) NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: report of symptoms consistent with hypoglycaemia and glucose of lower than 3 mmol/L before treatment of the episode Grp1: 1 (1) NA p NR Grp2: 5 (3) 9 NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Sitagliptin + placebo Fixed (100 mgimplies fixed daily	Def: report of symptoms consistent with hypoglycaemia and glucose of lower					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	than 3 mmol/L before treatment of the episode Grp1: 1 (1) NA p NR Grp2: 2 (1) 2 NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: report of symptoms consistent with hypoglycaemia and glucose of lower than 3 mmol/L before treatment of the episode Grp1: 5 (3) NA p NR Grp2: 2 (1) 2 NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: symptomatic episode with capillary or plasma glucose levels <3.5 mmol/l, irrespective of the need for external assistance; or an asymptomatic episode with capillary or plasma glucose levels <3.5 mmol/l that does not qualify as a major episode Grp1: 4 (4.4) NA p NR Grp2: 4 (4.4) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Russell-Jones, 2012[147] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: blood glucose <3.0 mmol/l Grp1: (19) NA p NR Grp2: (28) NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Pioglitazone + placebo Titrated (Max: 45 mgtarget dose 45 mg/d) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: symptoms of hypoglycemia that were treated by the patient or resolved on their own, with documented plasma glucose <3.0mmol/l Grp1: 0 NA p NR Grp2: 1 NA p NR					
Russell-Jones, 2012[147] RCT	Grp1:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: any time a patient felt that they had a sign or symptom, associated with concurrent blood glucose lower than 3Â·0 mmol/L, that was either selftreated by the patient or resolved independently Grp1: (2.5) Persons p <0.0001 Grp2: (18.8) Persons p					
Russell-Jones, 2012[147] RCT	Grp1:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically	Def: Defined as any time a patient felt that he or she had a					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	for sita) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	sign or symptom of hypoglycemia that was associated with concurrent blood glucose <3.0 mmol/L and that was either self-treated by the patient or resolved independently Grp1: 13 (8) Persons p <0.001 Grp2: 51 (32) Persons p					
Russell-Jones, 2012[147] RCT	Grp1:Sitagliptin + placebo Fixed (100 mgimplies fixed daily dose and makes sense clinically for sita) Grp2:Exenatide + placebo Fixed (2.0 mg subcut weeklyEQW) ITT:Yes Mode of AE collection:Active Followup (wks):26	Def: symptomatic + Plasma glucose <= 50mg/dl Grp1: 0 p Grp2: 2 p					
Schernthaner, 2015[148] RCT	Grp1: Metformin + glimepiride + placebo Mean: 1572 mg/d Titrated (Mean: 3.3 mg/d Max: 6 mg/d) Grp2: Metformin + saxagliptin + placebo Mean: 1647 Fixed 5mg/d	Def: confirmed (PG <3 mmol/l with or without symptoms) OR severe hypoglycemia (required assistance with or without PG <3mmol/l) Grp1: NR (10.5%) Grp2: NR Def: any hypoglycemia Grp1: 125 (34.8) Grp2: 21 (5.8)		Def: CHF, not defined Incidence Grp1: 6 Incidence Grp2: 1		Def: Diarrhea Grp1: 19 (5.3) Grp2: 15 (4.2)	Def: cancer: neoplasm cases Grp1: NR Grp2: NR Def: pancreatitis, not defined Grp1: 0 Grp2: 0

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
		Def: confirmed (PG <3 mmol/l regardless of symptoms) or severe (required assistance with or without PG <3 mmol/l) Grp1: NR (15.3) Grp2: NR (1.1) Def: confirmed (PG<3 mmol/l with or without symptoms) OR severe (requiring assistance with or without PG <3 mmol/l) Grp1: NR (18.5) Grp2: NR					
Schernthaner, 2004[149] RCT	Grp1: Metformin Varied Start: 850 mg, Max: 2550 mg Grp2: Pioglitazone Varied Start: 35 mg, Max: 45 mg					Def: Diarrhea; Nausea Grp1: (11.1); (4.2) Grp2: (3.2); (2.3)	
Schumm-Draeger, 2015[151]	Grp1: Metformin + placebo Fixed (adjusted to 1500, 2000, 2500 mg/d) Grp2: Metformin + dapagliflozin Fixed (adjusted to 1500, 2000, 2500 mg/d) Fixed 5 mg twice daily)	Def: severe Grp1: 0 Grp2: 0 Def: total Grp1: 0 Grp2: 0	Def: hepatic impairment Grp1: 0 Grp2: 0		Def: hip fracture Grp1: 0 Grp2: 0	Def: not specified Grp1: NR Grp2: NR	Def: volume depletion Grp1: 0 Grp2: 0 Def: Impaired renal

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
							function – AE terms of renal Grp1: NR Grp2: NR Def: UTI – events suggestive of UTI Grp1: 3(3) Grp2: 5(5) Def: Genital or mycotic infections Grp1: 1(1) Grp2: 5(5) Def: Impaired renal function – eGFR Grp1: NR Grp2: NR
Schumm-Draeger, 2015[151]	Grp1: Metformin + placebo Fixed (adjusted to 1500, 2000, 2500 mg/d) Grp2: Metformin + dapagliflozin Fixed (adjusted to 1500, 2000, 2500 mg/d) Fixed 10 mg/d	Def: severe Grp1: 0 Grp2: 0 Def: total Grp1: 0 Grp2: 2	Def: hepatic impairment Grp1: 0 Grp2: 0		Def: hip fracture Grp1: 0 Grp2: 0	Def: not specified Grp1: NR Grp2: NR	Def: volume depletion Grp1: 0 Grp2: 0 Def: Impaired renal function – AE terms of renal Grp1: NR Grp2: NR

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
							Def: UTI – events suggestive of UTI Grp1: 3(3) Grp2: 3(3) Def: Genital of mycotic infections Grp1: 1(3) Grp2: 1(3) Def: impaired renal function – eGFR Grp1: NR Grp2: NR
Scott, 2007[152] RCT	Grp1: Glipizide Varied, glucose: <160 mg/dl Start: 5 mg, Max: 20 mg D: 6 wks Grp2: Sitagliptin Fixed Start: 5 mg bid to 50 mg bid	Def: Mild or moderate Grp1: 21 (17.1) Grp2: 0 (0)					
Scott, 2008[153] RCT	Grp1: Metformin Fixed Start: >1500 mg D: 10 wks Grp2: Metformin + rosiglitazone Fixed Start: >1500 mg; Start: 8 mg, Mean: 8 mg D: 10 wks	Def: Mild or moderate Coll: NR Timing: Unspecified Grp1: 2 (2) Grp2: 1 (1)				Def: Diarrhea, nausea, abdominal pain, vomiting Coll: NR Timing: Unspecified ITT: No	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						Grp1: (9) Grp2: (7)	
Scott, 2008[153] RCT	Grp1: Metformin Fixed Start: ≥1500 mg Grp2: Metformin + sitagliptin Fixed Start: ≥1500 mg; Start: 100 mg	Def: Mild or moderate Coll: NR Timing: Unspecified ITT: No Grp1: 2 (2) Grp2: 1 (1)				Def: Diarrhea, nausea, abdominal pain, vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (9) Grp2: (1)	
Scott, 2008[153] RCT	Grp1: Metformin + rosiglitazone Fixed Start: > 1500 mg; Mean: 8 mg D: 10 wks Grp2: Metformin + sitagliptin Fixed Start: > 1500 mg; Mean: 100 mg D: 10 wks	Def: Mild or moderate Coll: NR Timing: Unspecified ITT: No Grp1: 1 (1) Grp2: 1 (1)				Def: Diarrhea, nausea, abdominal pain, vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (7) Grp2: (1)	
Seck, 2010[154] RCT	Grp1: Metformin + sitagliptin Fixed NR Grp2: Metformin + glipizide Fixed; Varied NR; Start: 5 mg, Max: 20 mg; Mean: 9.2 mg	Coll: Active Timing: Specified ITT: Yes Grp1: Severe: 18 (3) Mild/moderate: 31 (5.3) Grp2: Severe: 2 (<1) Mild/moderate: 199 (34.1)					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Seino, 2010[155] RCT	Grp1: Glibenclamide Varied, prespecified dose Start: 1.25 mg; Max: 2.5 mg D: 4 wks Grp2: Liraglutide Varied, prespecified dose Start: 0.3 mg; Max: 0.9 mg D: 2 wks	Coll: Passive Timing: Unspecified ITT: No Grp1: Symptoms: 45 (34.1); 228 events; IR: 3.927/year Severe: 0 (0) Grp2: Symptoms: 36 (13.4) 61 events; IR: 0.525/year Severe: 0 (0)				Def: Diarrhea; Constipation Coll: NR Timing: Unspecified ITT: No Grp1: (3.8; 3.8) Grp2: (6.3; 5.6)	Def: Pancreatitis Coll: NR Timing: Unspecified ITT: No Grp1: 0 (0) Grp2: 0 (0)
Shihara, 2011[157] RCT	Grp1:Pioglitazone Titrated (Mean: 23.24 mgMax: 30mg for women-45mg for menstarting 15mg/d) Grp2:SU Titrated (Mean: 23.24Max: 6mg/dstarting 0.5mg/d) ITT:No Mode of AE collection:Active Followup (wks):24	Def: self-treated plasma glucose < 3.1 mmol/l (56 mg/dl) Grp1: (26) 1Person-years p Grp2: (12) 0.21 1 Person-years p <0.0001					
Srivastava, 2012[158] RCT	Grp1:Metformin + glimepiride Fixed (kept at starting dose (dose on prior to study)) Titrated (Max: 4 mg/daystarted at 1-2 mg/day) Grp2:Metformin + sitagliptin Fixed (metformin dose prior to the study kept constant) Titrated (Max: 200 mg/daystarted at 50/100 mg/day) ITT:Yes Mode of AE collection: NR/unclear	Def: self-treated plasma glucose < 3.1 mmol/l (56 mg/dl) Grp1: (26) 1Person-years p Grp2: (10) 0.22 1 Person-years p <0.0001					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):						
St John Sutton, 2002[159] RCT	Grp1: Rosiglitazone Fixed Start: 4 mg Grp2: Glyburide Varied Start: NR, Max: 20 mg D: 8 wks	Def: Signs and symptoms Grp1: (1.9) Grp2: (7.1)		Def: NR Grp1: 1 (1.0) Grp2: 0 (0)			
Stewart, 2006[160] RCT	Grp1: Metformin Varied, prespecified Start: 500 mg, Max: 3000 mg, Mean: 2627.9 mg D: 20 wks Grp2: Metformin + rosiglitazone Varied, prespecified Start: 500 mg, Max: 2000 mg, Mean: 1812.2 mg; Start: 4 mg, Max: 8 mg, Mean: 6.8 mg D: 18 wks; 16 wks	Def: Mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 10 (4) Grp2: 17 (7)				Def: Diarrhea Grp1: (18) Grp2: (8)	
Tan, 2004[162] RCT	Grp1: Pioglitazone Varied Start: 30 mg, Max: 45 mg Grp2: Glibenclamide Varied Start: 1.75 mg, Max: 10.5 mg	Def: Symptoms or SMBG < 50 mg/dl Grp1: 4 (4) Grp2: 32 (29)					
Taskinen, 2011[164] RCT	Grp1:Metformin + placebo Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Grp2:Metformin + linagliptin Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Fixed (5mg) ITT:Yes	Def: moderate: discomfort enough to cause some interference with usual activity Grp1: (12.5) NA p NR Grp2: (23.4) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Passive Followup (wks):24						
Taskinen, 2011[164] RCT	Grp1:Metformin + placebo Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Grp2:Metformin + linagliptin Fixed (the same dosage of met as before they participated in the study (>=1500 mg or max tolerated dose)) Fixed (5mg) ITT:Yes Mode of AE collection:Passive Followup (wks):24	Def: Unspecified AE Grp1: 2 (1.4) NA p NR Grp2: 0 (0) NA p NR					
Tosi, 2003[167] RCT	Grp1: Metformin Varied Start: 500 mg, Max: 3000 mg Grp2: Metformin + glibenclamide Varied Start: 500 mg, Max: 2000; Start: 2.5 mg, Max: 10mg	Grp1: Severe: 2 (10.5), Mild or moderate: 1 (5) Grp2: NR				Def: Diarrhea + constipation + discomfort and abdominal pain and anorexia Grp1: (10.5) Grp2: (2.6)	
Umpierrez, 2006[170] RCT	Grp1: Metformin + pioglitazone Varied, glucose: <120 mg/dl, HbA1c: <8.0% Start: 1.54 g, Max: 1.57 g; Start: 30 mg, Max: 45 mg Grp2: Metformin + glimepiride Varied, glucose: <120 mg/dL	Def: mild or moderate Coll: Active Timing: Specified ITT: Yes Grp1: 10 (9) Grp2: 32 (33)				Def: Diarrhea Coll: Active Timing: Specified ITT: Yes	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Start: 1.47 g, Max: 1.49 g; Start: 2 mg, Max: 8 mg D: NR, 6 wks					Grp1: (4.7) Grp2: (6)	
Umpierrez, 2014[171] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 0.75mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 5 (3.4) NA p NR Grp2: 0 (0) NA p NR					
Umpierrez, 2014[171] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 1.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 2 (1.4) NA p NR Grp2: 5 (3.5) NA p NR					
Umpierrez, 2014[171] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability)	Def: Unspecified AE Grp1: 2 (1.4) NA p NR Grp2: 0 (0) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 0.75mg) ITT:Yes Mode of AE collection:Active Followup (wks):52						
Umpierrez, 2014[171] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 1.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 5 (3.4) NA p NR Grp2: 5 (3.5) NA p NR					
Umpierrez, 2014[171] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 0.75mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Def: Unspecified AE Grp1: 5 (3.4) NA p NR Grp2: 0 (0) NA p NR					
Umpierrez, 2014[171] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg/dayprogressively titrated up	Def: Unspecified AE Grp1: 0 (0) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	to 2000mg/day during the first 4 wks of treatment, or at least 1500mg/day depending upon tolerability) Grp2:Dulaglutide + placebo Fixed (once-weekly subcutaneously injected 1.5mg) ITT:Yes Mode of AE collection:Active Followup (wks):52	Grp2: 5 (3.5) NA p NR					
van der Meer, 2009[172] RCT	Grp1: Metformin + glimepiride Fixed; Varied Start: 1000 mg, Max: 2000 mg; NR D: NR; 8 wks Grp2: Pioglitazone + glimepiride Fixed, Varied Start: 15 mg, Max: 30 mg; NR D: 2 wks; NR			Grp1: 0 (0) Grp2: 0 (0)			
Wang, 2015[173] RCT	Grp1: Metformin + placebo Fixed (>=1500 mg/day or maximum tolerated dose mose patients (about 90%) had mean daily metformin dose >1500 mg) Grp2: Metformin + linagliptin Fixed (>=1500 mg/day or max tolerated dose most patients (about 90%) had >1500 mg/day dose) Fixed 5mg	Def: total, investigator-defined hypoglycemia: asymptomatic or symptomatic with glucose <=70 and included severe episodes Grp1: 1 (1) Grp2: 4.1 (2) Def: severe, requiring another persons assistance for active admin of resuscitative actions Grp1: 0 Grp2: 0	Def: alanine transaminase increase (unclear how much the increase was) that was considered drug related Grp1: 0 Grp2: 1	Def: stated hospitalized for CHF OR worsening CHF Grp1: 0 Grp2: 0	Def: non-hip fracture Grp1: 0 Grp2: 1		Def: pancreatitis Grp1: 0 Grp2: 0 Def: gastric cancer – not considered drug related Grp1: 0 Grp2: 1 Def: renal failure Grp1: 0 Grp2: 0

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
							Def: cholecystitis – not considered drug related Grp1: 1 Grp2: 0 Def: pancreatic cancer Grp1: 0 Grp2: 0
Weir, 2011[227] Retrospective cohort	Grp1:Metformin Not specified Grp2:Glyburide Not specified ITT:Not applicable (e.g., cohort) Mode of AE collection:Active Followup (wks):	Def: Unspecified AE Grp1: 0 (0) NA p NR Grp2: 0 (0) NA p NR					
Weir, 2011[227] Retrospective cohort	Grp1:Metformin Not specified Grp2:Glyburide Not specified ITT:Not applicable (e.g., cohort) Mode of AE collection:Active Followup (wks):	Def: minor - self treated hypoglycemia Grp1: Person-years p Grp2: 0.19 Person-years p					
Weir, 2011[227] Retrospective cohort	Grp1:Metformin Not specified Grp2: + basal insulin ITT:Not applicable (e.g., cohort) Mode of AE collection:Active Followup (wks):	Def: symptoms-only hypoglycemia Grp1: Person-years p NR Grp2: 0.51 Person-years p NR					
Weir, 2011[227] Retrospective cohort	Grp1:Metformin Not specified Grp2: + basal insulin ITT:Not applicable (e.g., cohort)	Def: symptomatic hypoglycemia: symptoms consistent with					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):	hypoglycemia and resolved shortly after oral glucose ingestion Grp1: 19 NA p Grp2: 10 NA p 0.01					
Weir, 2011[227] Retrospective cohort	Grp1:Glyburide Not specified Grp2: + basal insulin ITT:Not applicable (e.g., cohort) Mode of AE collection:Active Followup (wks):	Def: symptomatic and blood glucose < 60mg/dl Grp1: 1 NA p NR Grp2: 0 NA p NR					
Weir, 2011[227] Retrospective cohort	Grp1:Glyburide Not specified Grp2: + basal insulin ITT:Not applicable (e.g., cohort) Mode of AE collection:Active Followup (wks):	Def: symptomatic and blood glucose < 60mg/dl Grp1: 1 NA p NR Grp2: 1 NA p NR					
Weissman, 2005[174] RCT	Grp1: Metformin Varied Start: 500 mg bid, Max: 1000 mg bid Grp2: Metformin + rosiglitazone Fixed Start: 2500 mg; Start: 12 mg	Def: Mild or moderate Grp1: 4 (1) Grp2: 4 (1)				Def: Withdrawn due to GI Grp1: (6.8) Grp2: (3.1)	
White, 2014[175] RCT	Grp1:Metformin + placebo Fixed (fixed dose metformin at >=1500 mg) Grp2:Metformin + saxagliptin Fixed (fixed dose but could be >=1500 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):	Def: symptomatic or asymptomatic and blood glucose < 50mg/dl Grp1: 0 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
White, 2014[175] RCT	Grp1:Metformin + placebo Fixed (fixed dose metformin at >=1500 mg) Grp2:Metformin + saxagliptin Fixed (fixed dose but could be >=1500 mg) Fixed (5 mg) ITT:Yes Mode of AE collection:Active Followup (wks):	Def: symptomatic or asymptomatic and blood glucose < 50mg/dl Grp1: 0 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2009[176] RCT	Grp1: Metformin Fixed Mean: 1000 mg or 2000 mg Grp2: Sitagliptin Fixed Mean: 100 mg	Def: Coll: Active Timing: Unspecified ITT: No Grp1: 2 (1) Grp2: 2 (1)				Def: Nausea; Diarrhea; Abdominal pain; Vomiting; Nausea/ Vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (3; 7; 4; 0; 20 for 1000 mg and 10; 12; 6; 3; 31 for 2000 mg) Grp2: (1; 4; 5; 1; 20)	
Williams-Herman, 2009[176] RCT	Grp1: Metformin Fixed Mean: 1000 mg bid Grp2: Metformin + sitagliptin	Def: Mild or moderate Coll: Active Timing: Unspecified				Def: Nausea; vomiting; diarrhea;	

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed Mean: 500 mg bid; Mean: 50 mg bid	ITT: No Grp1: 2 (1) Grp2: 4 (2)				abdominal pain; Nausea/ Vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (3; 0; 7; 4; 31) Grp2: (5; 2; 9; 3; 26)	
Williams-Herman, 2009[176] RCT	Grp1: Metformin Fixed Mean: 1000 mg bid Grp2: Metformin + sitagliptin Fixed Mean: 1000 mg bid; Mean: 50 mg bid	Def: Mild or moderate Coll: Active Timing: Unspecified ITT: No Grp1: 2 (1) Grp2: 5 (3)				Def: Nausea; vomiting; diarrhea; abdominal pain; Nausea/ Vomiting Coll: NR Timing: Unspecified ITT: No Grp1: (3; 0; 7; 4; 31) Grp2: (NR; 4; 13; 4; 29)	
Williams-Herman, 2010[177]	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Sitagliptin + placebo	Def: either symptomatic episode with					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	capillary or plasma glucose levels < 3.5 mmol/L, irrespective of the need for external assistance or an asymptomatic episode with capillary or plasma glucose levels < 3.5 mmol/L that does not qualify as a major e Grp1: 173 (42.4) 408Persons p Grp2: 10 (2.5) 406 Persons p					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 1000 mg) Grp2:Sitagliptin + placebo Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: other - symptoms suggestive of hypoglycemia but without confirmative measurement Grp1: 45 (11) 408Persons p NR Grp2: 8 (2) 406 Persons p NR					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Sitagliptin + placebo Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: plasma glucose <= 70 mg/dl and/or symptoms and/or signs attributable to hypoglycemia Grp1: Person-years p NR Grp2: (4.8) 0.1 1 Person-years p NR					
Williams-Herman,	Grp1:Metformin + placebo Titrated (Max: 2000 mg)	Def: plasma glucose <= 70 mg/dl and/or					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
2010[177] RCT	Grp2:Sitagliptin + placebo Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	symptoms and/or signs attributable to hypoglycemia Grp1: Person-years p NR Grp2: (5.3) 0.3 1 Person-years p NR					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 1000 mg) Grp2:Sitagliptin + placebo Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: plasma glucose <= 70 mg/dl and/or symptoms and/or signs attributable to hypoglycemia Grp1: Person-years p NR Grp2: (10.2) 0.4 1 Person-years p NR					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Sitagliptin + placebo Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: plasma glucose <= 70 mg/dl and/or symptoms and/or signs attributable to hypoglycemia Grp1: (4.8) 1Person-years p NR Grp2: (5.3) 0.3 1 Person-years p NR					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: plasma glucose <= 70 mg/dl and/or symptoms and/or signs attributable to hypoglycemia Grp1: (4.8) 1Person-years p NR Grp2: (10.2) 0.4 1 Person-years p NR					
Williams-	Grp1:Metformin + placebo	Def: mild or					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Herman, 2010[177] RCT	Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	moderate nature' Grp1: p Grp2: 5 p					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 1000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 0 NA p NR Grp2: 0 NA p NR					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 1000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 5 NA p NR Grp2: 0 NA p NR					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 2 NA p NR					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 2 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Mode of AE collection:Active Followup (wks):104						
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 0 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 0 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 1000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 5 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 1000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 5 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2010[177]	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin	Def: hypoglycemic episodes - Asymptomatic, blood					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
RCT	Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	glucose<70mg/dl Grp1: 2 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2010[177] RCT	Grp1:Metformin + placebo Titrated (Max: 2000 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 2 NA p NR					
Williams-Herman, 2010[177] RCT	Grp1:Sitagliptin + placebo Titrated (Max: 100 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 1 NA p NR					
Williams-Herman, 2010[177] RCT	Grp1:Sitagliptin + placebo Titrated (Max: 100 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 2 NA p NR					
Williams-Herman, 2010[177] RCT	Grp1:Sitagliptin + placebo Titrated (Max: 100 mg) Grp2:Metformin + sitagliptin Titrated (Max: 1000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 1 NA p NR Grp2: 0 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
Williams-Herman, 2010[177] RCT	Grp1:Sitagliptin + placebo Titrated (Max: 100 mg) Grp2:Metformin + sitagliptin Titrated (Max: 2000 mg) Titrated (Max: 100 mg) ITT:No Mode of AE collection:Active Followup (wks):104	Def: hypoglycemic episodes - Symptomatic, blood glucose<70mg/dl Grp1: 1 NA p NR Grp2: 0 NA p NR					
Wright, 2006[228] RCT	Grp1: Metformin Varied, glucose: <6 mmol/L Max: 2550 mg Grp2: Sulfonylurea Varied, glucose: <6 mmol/L Max: glipizide 40 mg, chlorpropramide 500 mg, glibenclamide 20 mg	Def: Mean annual % Coll: Active Timing: Specified ITT: NR Grp1: Substantive hypo: 0.3, (CI: 0.1-1.1); Any: 1.7, (CI: 1-3) Grp2: Substantive hypo: 1.2, (CI: 0.4-3.4); Any: 7.9, (CI: 5.1-11.9)					
Xu, 2015[178]	Grp1: Pioglitazone Titrated 45 mg/d Grp2: Exenatide Titrated 10 ug twice daily	Def: mild Grp1: 5(NR) Grp2: 13(NR) Def: severe Grp1: 0(NR) Grp2: 0(NR)				Def: nausea Grp1: 1(NR) Grp2: 37(NR) Def: vommitting Grp1: 1(NR) Grp2: 15(NR) Def: diarrhea Grp1: 4(NR)	Def: descreased vision Grp1: 3(NR) Grp2: 2(NR) Def: severe allergic reaction Grp1: 0(NR) Grp2: 0(NR) Def: pancreatiti

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
						Grp2: 6(NR) Def: constipation Grp1: 1(NR) Grp2: 6(NR)	s Grp1: 0(NR) Grp2: 1(NR) Def: cancer Grp1: 0(NR) Grp2: 1(NR)
Yamanouchi, 2005[179] RCT	Grp1: Metformin Fixed Start: 750 mg Grp2: Pioglitazone Fixed Start: 30 mg women, 45 mg men	Def: NR Grp1: 0 (0) Grp2: 0 (0)					
Yamanouchi, 2005[179] RCT	Grp1: Metformin Fixed 750 mg Grp2: Glimepiride Varied Start: 1.0 mg, Max: 2.0 after 1 month in 8 cases. Rest on 1 mg	Grp1: Severe: 0 (0); Mild/moderate: 0 (0) Grp2: Severe: 0 (0); Mild/moderate: 1 (2.7)					
Yamanouchi, 2005[179] RCT	Grp1: Pioglitazone Fixed Start: 30 mg for women and 45 mg for men Grp2: Glimepiride Varied Start: 1.0 mg, Max: 2.0	Grp1: Serious: 0 (0), Mild or moderate: 0 (0) Grp2: Serious: 0 (0), Mild or moderate: 1 (2.7)					
Yang, 2011[180] RCT	Grp1:Metformin + placebo Fixed (Mean: 1606 mg/dcontd pre-study dose: 1500 - 3000 mg/d) Grp2:Metformin + saxagliptin	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 1 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Fixed (Mean: 1620 mg/dcontd on prestudy dose - 1500 - 3000 mg/d) Fixed (5 mg/d) ITT:Yes Mode of AE collection:Active Followup (wks):24	Grp2: 2 NA p NR					
Yang, 2011[180] RCT	Grp1:Metformin + placebo Fixed (Mean: 1606 mg/dcontd pre-study dose: 1500 - 3000 mg/d) Grp2:Metformin + saxagliptin Fixed (Mean: 1620 mg/dcontd on prestudy dose - 1500 - 3000 mg/d) Fixed (5 mg/d) ITT:Yes Mode of AE collection:Active Followup (wks):24	Def: hypoglycemic episodes - Asymptomatic, blood glucose<70mg/dl Grp1: 2 NA p NR Grp2: 2 NA p NR					
Yang, 2011[181] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Fixed (0.6mg daily) ITT:No Mode of AE collection:Active	Def: total incidence of pateints with either of the MedDRA terms'hypoglycaemia' Grp1: (2.3) NA p NR Grp2: (0.9) NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Followup (wks):16						
Yang, 2011[181] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.2 mg1.2 mg target, started at 0.6 mg/day) ITT:No Mode of AE collection:Active Followup (wks):16	Def: plasma glucose concentration < 54mg/dl (3.0mmol/l) Grp1: 0 NA p NR Grp2: 0 NA p NR					
Yang, 2011[181] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.8 mg/dtarget 18	Def: signs or symptoms associated with blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 0 Persons p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	mg; started at 0.6 mg and up-titrated) ITT:No Mode of AE collection:Active Followup (wks):16						
Yang, 2011[181] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Fixed (0.6mg daily) ITT: NR Mode of AE collection:Active Followup (wks):16	Def: signs or symptoms associated with blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 0 Persons p					
Yang, 2011[181] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on	Def: signs or symptoms associated with blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 5 (2) Persons p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.2 mg1.2 mg target, started at 0.6 mg/day) ITT: NR Mode of AE collection:Active Followup (wks):16						
Yang, 2011[181] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.8 mg/dtarget 18 mg; started at 0.6 mg and up-titrated) ITT: NR Mode of AE collection:Active Followup (wks):16	Def: signs or symptoms associated with blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 0 Persons p					
Yang, 2011[181] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks)	Def: signs or symptoms associated with blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 5 (2)					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Fixed (0.6mg daily) ITT: NR Mode of AE collection:Active Followup (wks):16	Persons p					
Yang, 2011[181] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.2 mg1.2 mg target, started at 0.6 mg/day) ITT: NR Mode of AE collection:Active Followup (wks):16	Def: signs or symptoms associated with blood glucose ,3.0 mmol/L (either self-treated or resolved independently) Grp1: 0 Persons p Grp2: 5 (2) Persons p					
Yang, 2011[181] RCT	Grp1:Metformin + glimepiride + placebo Titrated (2000 mg/daycould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 4 mg/daystarted	Def: plasma glucose concentration<=3.9 mmol/l, of mild intensity and not requiring assistance Grp1: 5 NA p NR Grp2: 3 NA p NR					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	with 1 mg and titrated over 2 weks) Grp2:Metformin + liraglutide + placebo Titrated (2000 mg/dcould down-titrate to 1500 mg/d based on GI side effects; dc'd from trial if <1500 mg/d) Titrated (Max: 1.8 mg/dtarget 18 mg; started at 0.6 mg and up-titrated) ITT: NR Mode of AE collection:Active Followup (wks):16						
Yang, 2012[182] RCT	Grp1:Metformin + placebo Fixed (1000 or 1700 mg/d) Grp2:Metformin + sitagliptin Fixed (1000 or 1700 mg/d) Fixed (100 mg/d) ITT:No Mode of AE collection:Active Followup (wks):	Def: NR but sppears to be self report Grp1: 1 (1.2) Persons p NR Grp2: 4 (5.4) Persons p NR					
Yang, 2012[182] RCT	Grp1:Metformin + placebo Fixed (1000 or 1700 mg/d) Grp2:Metformin + sitagliptin Fixed (1000 or 1700 mg/d) Fixed (100 mg/d) ITT: NR Mode of AE collection:Active Followup (wks):24	Def: symptoms not confirmed with BG Grp1: 4 p Grp2: 4 p					
Yoon, 2011[183] RCT	Grp1:Metformin Titrated (Mean: 1234.2 mgMax: 2000 mg/dstarted at 500 mg/d and titrated) Grp2:Rosiglitazone Titrated (Mean: 5.9 mgMax: 8 mg/dstarted at 4 mg in am)	Def: symptoms with confirmed with BG <= 2.8 Grp1: 0 p Grp2: 0 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	ITT:No Mode of AE collection:Active Followup (wks):48						
Yoon, 2011[183] RCT	Grp1:Metformin Titrated (Mean: 1234.2 mgMax: 2000 mg/dstarted at 500 mg/d and titrated) Grp2:Glimepiride Titrated (Mean: 4.5 mg/dMax: 8 mg/dstarted at 2 mg in am) ITT:No Mode of AE collection:Active Followup (wks):48	Def: symptoms and PG<3.1 mmol/l and self-treated Grp1: Person-years p Grp2: 0.09 Person-years p <0.0001					
Yoon, 2011[183] RCT	Grp1:Rosiglitazone Titrated (Mean: 5.9 mgMax: 8 mg/dstarted at 4 mg in am) Grp2:Glimepiride Titrated (Mean: 4.5 mg/dMax: 8 mg/dstarted at 2 mg in am) ITT:No Mode of AE collection:Active Followup (wks):48	Def: symptoms and PG<3.1 mmol/l and self-treated Grp1: Person-years p Grp2: 0 Person-years p <0.0001					
Yuan, 2012[184] RCT	Grp1:Metformin Titrated (started at 1000mg for 4 wks, 1500mg for 4-12 wks; if FPG>5.1mmol/l at week 12, met was increased to 2000mg; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be de Grp2:Exenatide Titrated (started at 10ug for 4 wks, 20ug for 4-12 wks without hypoglycemia; 1 confirmed hypoglycemic event	Def: symptoms and PG<3.1 mmol/l and self-treated Grp1: Person-years p Grp2: 0.09 Person-years p <0.0001					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	(documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be decreased 50% (additional episodes allowed ITT:Yes Mode of AE collection:Passive Followup (wks):26						
Yuan, 2012[184] RCT	Grp1:Metformin Titrated (started at 1000mg for 4 wks, 1500mg for 4-12 wks; if FPG>5.1mmol/l at week 12, met was increased to 2000mg; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be de Grp2:Exenatide Titrated (started at 10ug for 4 wks, 20ug for 4-12 wks without hypoglycemia; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be decreased 50% (additional episodes allowed ITT:Yes Mode of AE collection:Passive Followup (wks):26	Def: Unspecified AE Grp1: Person-years p NR Grp2: 0.46 Person-years p NR					
Yuan, 2012[184] RCT	Grp1:Metformin Titrated (started at 1000mg for 4 wks, 1500mg for 4-12 wks; if FPG>5.1mmol/l at week 12, met was increased to 2000mg; 1 confirmed hypoglycemic event	Def: Unspecified AE Grp1: 1 p <0.05 Grp2: 4 p					

Author, year Study design	Intervention	Hypoglycemia, n (%)	Liver failure, n (%)	Congestive heart failure, n (%)	Fractures, n (%)	GI side effects, n (%)	Other, n (%)
	(documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be de Grp2:Exenatide Titrated (started at 10ug for 4 wks, 20ug for 4-12 wks without hypoglycemia; 1 confirmed hypoglycemic event (documented blood glucose < 3.3mmol/l) and 2 unconfirmed hypoglycemic events allowed met dose to be decreased 50% (additional episodes allowed ITT:Yes Mode of AE collection:Passive Followup (wks):26						

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not Reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.

Table D13. Quality of studies evaluating safety of diabetes medications

Author, year	Randomized study	Randomization scheme	Double-blind	Blinding method	Dropouts description
Ahren, 2014[2]	Yes	Not described	Yes	Yes	Yes
Alba, 2013[3]	Yes	Yes	Yes	Not described	Yes
Arechavaleta, 2011[5]	Yes	Yes	Yes	Not described	Yes
Arjona Ferreira, 2013[6]	Yes	Yes	Yes	Yes	Yes
Aschner, 2012[8]	Yes	Yes	No	Not described	Yes
Bailey, 2013[10]	Yes	Yes	Yes	Yes	Yes
Barnett, 2012[13]	Yes	Yes	Yes	Yes	Yes
Bergenstal, 2010[14]	Yes	Yes	Yes	Yes	Yes
Bergenstal, 2012[15]	Yes	Yes	Yes	Yes	Yes
Bolinder, 2012[17]	Yes	Yes	Yes	Yes	Yes
Borges, 2011[18]	Yes	Not described	Yes	Not described	No
Cefalu, 2013[20]	Yes	Yes	Yes	Yes	Yes
Chawla, 2013[23]	Yes	Yes	NR	Not described	Yes
Davies, 2013[218]	Yes	Yes	No	Not described	Yes
DeFronzo, 2005[28]	Yes	Yes	Yes	Yes	Yes
DeFronzo, 2012[31]	Yes	Not described	Yes	Yes	No
Del Prato, 2015[32]	Yes	Not described	Yes	Not described	No
Del Prato, 2014[33]	Yes	Not described	Yes	Yes	Yes
Derosa, 2013[42]	Yes	Yes	Yes	Yes	Yes
Derosa, 2013[43]	Yes	Yes	Yes	Yes	Yes
Diamant, 2010[44]	Yes	Yes	No	Not described	Yes
Erem, 2014[47]	Yes	Not described	No	Not described	No
Esposito, 2011[48]	Yes	Yes	Yes	Yes	Yes
Ferrannini, 2013[53]	Yes	No	No	Not described	No
Ferrannini, 2013[194]	Yes	Yes	No	Yes	No
Fonseca, 2012[56]	Yes	Yes	Yes	Not described	Yes
Forst, 2010[57]	Yes	Yes	Yes	Yes	Yes
Forst, 2014[59]	Yes	Not described	No	Not described	Yes
Gallwitz, 2011[60]	Yes	Not described	No	Not described	No
Gallwitz, 2012[61]	Yes	Yes	Yes	Yes	Yes

Author, year	Randomized study	Randomization scheme	Double-blind	Blinding method	Dropouts description
Gallwitz, 2012[62]	Yes	Yes	NR	Not desc--ribed	Yes
Garber, 2011[67]	Yes	Yes	No	Not described	Yes
Genovese, 2013[68]	Yes	Not described	Yes	Yes	Yes
Genovese, 2013[69]	Yes	Yes	Yes	Yes	Yes
Goke, 2010[70]	Yes	Yes	Yes	Yes	Yes
Gupta, 2013[76]	Yes	Yes	No	Not described	YES
Haak, 2012[77]	Yes	Not described	Yes	Not described	Yes
Haak, 2013[78]	Yes	Yes	Yes	Yes	Yes
Haring, 2014[83]	Yes	Yes	Yes	Yes	Yes
Henry, 2012[84]	Yes	Yes	Yes	Not described	No
Henry, 2012[84]	Yes	Yes	Yes	Not described	Yes
Hermans, 2012[87]	Yes	Not described	Yes	Not described	Yes
Hong, 2013[195]	Yes	Yes	Yes	Yes	Yes
Ji, 2015[93]	Yes	Not described	Yes	Not described	Yes
Kadoglou, 2011[95]	Yes	Not described	No	Not described	Yes
Kadowaki, 2013[96]	Yes	Yes	Yes	Yes	Yes
Kaku, 2011[99]	Yes	Not described	No	Not described	
Kim, 2014[103]	Yes	Not described	No	Not described	Yes
Lavalle-Gonzalez, 2013[106]	Yes	Yes	Yes	Yes	Yes
List, 2009[109]	Yes	Yes	Yes	Yes	Yes
Maffioli, 2013[111]	Yes	Yes	Yes	Yes	Yes
Moon, 2014[114]	Yes	Not described	No	Not described	Yes
Nauck, 2009[119]	Yes	Yes	Yes	Not described	Yes
Nauck, 2011[120]	Yes	Yes	Yes	Yes	Yes
Nauck, 2014[121]	Yes	Not described	Yes	Not described	Yes
Pfutzner, 2011[128]	Yes	Not described	Yes	Not described	No
Pfutzner, 2011[129]	Yes	Yes	Yes	Not described	Yes
Pratley, 2014[131]	Yes	Not described	Yes	Not described	Yes
Qiu, 2014[132]	Yes	Yes	Yes	Not described	Yes
Reasner, 2011[135]	Yes	Not described	Yes	Not described	Yes
Ridderstrale, 2014[136]	Yes	Yes	Yes	Yes	Yes

Author, year	Randomized study	Randomization scheme	Double-blind	Blinding method	Dropouts description
Roden, 2013[139]	Yes	Yes	Yes	Yes	Yes
Rosenstock, 2010[141]	Yes	Not described	Yes	Yes	Yes
Rosenstock, 2012[142]	Yes	Not described	Yes	Not described	Yes
Rosenstock, 2013[144]	Yes	Yes	Yes	Yes	Yes
Rosenstock, 2015[145]	Yes	Yes	Yes	Yes	Yes
Ross, 2012[146]	Yes	Yes	Yes	Yes	Yes
Russell-Jones, 2012[147]	Yes	Yes	Yes	Yes	Yes
Schernthaner, 2015[148]	Yes	Yes	Yes	Not described	Yes
Schumm-Draeger, 2015[151]	Yes	Yes	Yes	Yes	Yes
Seino, 2012[156]	Yes	Yes	Yes	Yes	Yes
Shihara, 2011[157]	Yes	Yes	No	Not described	Yes
Skrivanek, 2014[226]	Yes	Not described	Yes	Not described	Yes
Taskinen, 2011[164]	Yes	Not described	Yes	Not described	Yes
Umpierrez, 2014[171]	Yes	Yes	Yes	Yes	Yes
Wang, 2015[173]	Yes	Yes	Yes	Yes	Yes
White, 2014[175]	Yes	Yes	Yes	Yes	Yes
Williams-Herman, 2010[177]	Yes	Yes	Yes	Yes	Yes
Xu, 2015[178]	Yes	Yes	No	No	Yes
Yang, 2011[180]	Yes	Yes	Yes	Not described	Yes
Yang, 2011[181]	Yes	Not described	Yes	Yes	Yes
Yang, 2012[182]	Yes	Yes	Yes	Yes	Yes
Yoon, 2011[183]	Yes	Not described	Yes	Not described	Yes
Yuan, 2012[184]	Yes	Yes	No	Not described	Yes

Table D14. Results from randomized controlled trials and observational studies reporting outcomes in a subpopulation

Subgroup	Outcome				
	HbA1c	**Weight**	**Cardiovascular events**	**Nephropathy**	**Other AEs**
Age	**Metformin vs. sitagliptin:**[7] **Metformin vs. alogliptin:**[131] **Pioglitazone vs. alogliptin**:[141] **Pioglitazone vs. sitagliptin:**[124] **Glipizide vs. sitagliptin:**[6] No age-treatment interaction **Metformin vs. metformin + DPP-4:**[2, 57, 61, 72, 96, 119, 131, 135, 175, 188] Favors combined therapy across age groups **Metformin vs. metformin + SU:**[2, 57, 61] Favors combined therapy across age groups **Metformin + TZD vs. metformin + DPP-4:**[31, 153] No age-treatment interaction **Metformin + SU vs. metformin + DPP-4:**[148 41187] No age-treatment interaction	No evidence	**Metformin vs. glyburide vs. glimepiride:**[199] Favors metformin and glimepiride over glyburide in patients age 51 or older, but only metformin for patients aged 30 to 50 **Metformin vs. SU**:[210] No interaction age-treatment	**Metformin vs. SU vs. Rosiglitazone:**[198] No interaction age-treatment	**<u>Hypoglycemia:</u>** **Metformin + SU vs. metformin + DPP4:**[5, 70] No age-treatment interaction **<u>Fractures:</u>** No evidence
Sex	**Metformin vs. sitagliptin:**[7] **Metformin vs. alogliptin:**[131] **Metformin vs. pioglitazone:**[50] **Pioglitazone vs. alogliptin:**[141]	**Metformin vs. pioglitazone:**[50] Favors metformin for weight control regardless of sex **Metformin vs. metformin + pioglitazone:**[231]	**<u>Cardiovascular events:</u>** **Metformin vs. glyburide vs. glimepiride**:[199] No interaction sex-treatment **Metformin vs. SU**:[210]	No evidence	**<u>Hypoglycemia:</u>** **Metformin + SU vs. metformin + DPP4:**[5, 232] No sex-treatment interaction

	Pioglitazone vs. sitagliptin:[124] **Glipizide vs. sitagliptin:**[6] No sex-treatment interaction **Metformin vs. metformin + DPP-4:**[2, 57, 72, 96, 119 , 131, 135, 175, 188] Favors combined therapy regardless of sex **Metformin vs. metformin + SU:**[2, 57, 61] Favors combined therapy regardless of sex **Metformin + TZD vs. metformin DPP-4:**[31, 153] No sex-treatment interaction	Favors metformin plus pioglitazone for weight control regardless of sex **Metformin vs. metformin + dapaglifozin:**[17] Increased weight loss for men with combined therapy	No interaction sex-treatment **<u>Death:</u>** **Metformin vs. glipizide vs. glibenclamide vs. rosiglitazone:**[214] No differences in death by treatment regardless of sex		**<u>Fractures:</u>** **Metformin vs. TZD vs. SU:**[219, 220] Glyburide and metformin favored over rosiglitazone or pioglitazone in pre- and post-menopausal women; difference in men unclear
Obesity	**Metformin vs. SU:**[169] Favors SU among obese patients in long-term treatment (over 9 years) **Metformin vs. sitagliptin:**[7] **Metformin vs. alogliptin:**[131] **Pioglitazone vs. alogliptin:**[141] **Glipizide vs. sitagliptin:**[6] No baseline BMI-treatment interaction **Metformin vs. metformin + rosiglitazone:**[202] Favors metformin + rosiglitazone among overweight and obese patients	**Metformin vs. SU:**[233] Obese patients lost more weight with metformin **Metformin vs. metformin + rosiglitazone:**[202] Favors metformin for weight loss among obese patients	No evidence	No evidence	No evidence

	Metformin vs. metformin + DPP-4:[2, 57, 72, 119, 131, 135] Favors combined therapy across BMI groups **Metformin vs. metformin + SU:**[2, 57, 61] Favors combined therapy across BMI groups **Metformin + TZD vs. metformin + DPP-4:**[31, 153] No baseline BMI-treatment interaction **Metformin + rosiglitazone vs. metformin + sitagliptin:**[153] No baseline BMI-treatment interaction **Metformin + dapagliflozin vs. metformin + glipizide:**[32] No baseline BMI-treatment interaction				
Race	**Metformin vs. sitagliptin:**[7] **Metformin vs. alogliptin:**[131] **Pioglitazone vs. alogliptin:**[141] **Glipizide vs. sitagliptin:**[6] No age-treatment interaction **Metformin vs. metformin + DPP-4:**[2, 57, 61, 72, 119 , 131, 135, 175] Favors combined therapy	No evidence	No evidence	**Metformin vs. SU vs. rosiglitazone:**[198] No race-treatment interaction **Metformin vs. metformin + DPP-4:**[173 41196] No race-treatment interaction	No evidence

	across age groups **Metformin vs. metformin + SU:**[2, 57, 61] Favors combined therapy across age groups **Metformin + TZD vs. metformin + DPP-4:**[31, 153]				

BMI = body mass index; CHF = congestive heart failure; HbA1c = hemoglobin A1c

The summary of results above is based on qualitative synthesis of the studies. Statistical significance for interactions is provided in the text if reported in the publication

Appendix E. Gray Literature

We searched the Food and Drug Administration (FDA) Web site for unpublished trials of the following drugs: albiglutide, alogliptin, canagliflozin, dapagliflozin, dulaglutide, empagliflozin, linagliptin, liraglutide, saxagliptin, pioglitazone and rosiglitazone. After reviewing the data from the FDA medical reviews and statistical reviews, we found 40 studies with drug comparisons of interest. Thirty-seven of these 40 trials were published in the peer-reviewed literature and were included in this report. The published data were consistent with the data described in the FDA reviews on select outcomes (HbA1c, hypoglycemia, and all-cause mortality). One trial was not published in the peer-reviewed literature until October 2014 and was therefore not included in this report.[234] Two trials were published only as meeting abstracts in 2014; therefore, they were not included in this report.[235]

Additionally, we found 38 unpublished studies from our search of the ClinicalTrials.gov registry. Fourteen of these studies were either ongoing or not yet open therefore no data was available. Twenty-four of these studies were completed and 10 of them had study results available on the website. We identified a clinical study registry that has been published and included in this report, but several of the long term outcomes were not included in its related publication.[2]

KQ1 Intermediate Outcomes

We found 10 unpublished reports from ClinicalTrials.gov that reported on HbA1c outcomes for our comparison of interest. These results were not entirely consistent with the results from the published studies included in the review.

Monotherapy Comparisons

Metformin Versus DPP-4 Inhibitors

Two short RCTs compared metformin with DPP-4 inhibitors. One RCT (NCT01289119) was an international multicenter phase-3 trial. The study had 98 participants in the metformin monotherapy arm (mean daily dose of 1484.2 mg) group, and 92 participants in the alogliptin monotherapy (25 mg daily) arm. The mean change from baseline in HbA1c at week 16 was -0.22 ± 0.065% (mean ± standard error) for metformin monotherapy group and was -0.99 ± 0.074% for alogliptin monotherapy group.

Another RCT (NCT01076088) was a multicenter phase 3 trial conducted in China. The study had 124 participants in the metformin monotherapy (1700 mg daily) group, and 120 participants in the sitagliptin monotherapy (100 mg daily) group. The mean change in HbA1c from baseline to week 24 was -1.6% (95% CI, -1.8% to -1.3%) for the metformin group and -0.99 (95% CI, -1.2% to -0.75%) for the sitagliptin monotherapy group.

Thiazolidinediones Versus DPP-4 Inhibitors

One unpublished 30-week RCT (NCT01183013) had 134 participants receiving 45mg of pioglitazone daily and 130 participants receiving 5mg of linagliptin. The mean change from baseline in HbA1c was -0.87 ± 0.09% (mean ± standard error) in the pioglitazone group, which exceeded than that in the linagliptin group (-0.39 ± 0.09%).

Thiazolidinediones Versus GLP-1 Agonists

One unpublished trial (NCT01147627) had 136 subjects in the pioglitazone 30 mg arm and 142 in the exenatide arm (10 μg twice daily titrated up to 20 μg twice daily). The mean change from baseline in HbA1c at week 48 was greater in the exenatide group (mean ± standard deviation, -1.8 ± 1.3%) than in the pioglitazone group (-1.5 ± 1.3%). This was inconsistent with the one published study included in this report.[147]

Sulfonylureas Versus DPP-4 Inhibitors

Two unpublished RCTs compared glimepiride (1 to 6 mg) with DPP-4 inhibitors in older patients, and both studies favored glimepiride over DPP-4 inhibitors. One trial (NCT01006603) evaluated glimepiride against 5 mg of saxagliptin daily. The study had 360 subjects in both arms and the mean change from baseline in HbA1c at week 52 was greater in the glimepiride arm than in the saxagliptin arm (-0.64% versus -0.44%). Another 30-week trial (NCT01189890) had 239 subjects in the glimepiride arm and 241 in the sitagliptin group. The between-group difference in change in HbA1c of 0.19% (95% CI, 0.03% to 0.34%) favored glimepiride over sitagliptin.

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Three RCTs lasting 4 to 6 months compared metformin with the combination of metformin plus a DPP-4 inhibitor. The results were consistent with the results from the published study, as all favored the combination arm. One unpublished 16-week trial (NCT01289119) reported statistically significant between-group difference in mean HbA1c change of -0.69% (95% CI, -0.87% to -0.51%; $P < 0.001$), favoring metformin plus 25mg of daily alogliptin (-0.91 ± 0.065%, n=99) over metformin monotherapy (-0.22 ± 0.065%, n=98). Another trial in China (NCT01076088) reported a greater decrease in mean HbA1c at week 24 in patients treated with 100 mg of sitagliptin daily as add-on therapy to metformin (-1.8%; 95% CI, -2.1% to -1.6%) compared with those treated with metformin monotherapy (-1.6%, 95% CI, -1.8% to -1.3%), after adjustment for differences between groups. Another trial (NCT00960076) randomized 144 participants to the metformin (2000 mg daily) group and 138 to the metformin (1500 mg daily) plus saxagliptin (5 mg daily) group, and favored the combination arm with a mean between-group difference in HbA1c from baseline to week 18 of -0.52% (95% CI, -0.73% to -0.31%).

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

One large, unpublished trial (NCT00856284) compared metformin plus 5 mg of glipizide to metformin plus 25 mg of alogliptin. The metformin plus alogliptin combination was not inferior to the metformin plus glipizide combination, with a mean between-group difference of -0.13%.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

One unpublished trial in Japan (NCT01368081) had 63 subjects treated with 500 mg of metformin as add-on therapy to background sulfonylurea, and 65 treated with empagliflozin at

25mg daily as add-on therapy to background metformin. Unlike the published study favoring the metformin plus SGLT-2 inhibitor combination group, the mean change from baseline in HbA1c was very similar for both the metformin plus sulfonylurea combination group (-0.97 ± 0.08%) and the metformin plus empagliflozin combination group (-0.98 ± 0.06%) after 52 weeks of treatment.

Combination of Metformin Plus a Basal Insulin Versus a Combination of Metformin Plus a Premixed Insulin

The combination of metformin and insulin detemir was evaluated against the combination of metformin and biphasic insulin aspart 30 in a 50-week RCT (NCT01068652). The study had 200 subjects in the metformin plus insulin detemir group and 203 in the metformin plus biphasic insulin aspart 30 group, and similar to previously published studies, reported no statistically-significant between-group difference in HbA1c at week 50 (0.11%; 95% CI, -0.12% to 0.34). The change in HbA1c from baseline was -1.2% in the metformin plus glipizide group, and -1.3% in the metformin plus alogliptin group.

KQ2 Long-Term Outcomes

We found nine unpublished reports from the ClinicalTrials.gov site and one clinical registry study that reported on long-term clinical outcomes for our comparisons of interest. These results were generally consistent with the results from the published studies included in the review.

Monotherapy Comparisons

Metformin Versus DPP-4 Inhibitors

One 24-week RCT (NCT01076088) evaluated sitagliptin against metformin, both as monotherapy. The study reported one case of cerebral infarction out of 120 participants in sitagliptin arm and no cases in the metformin group. One subarachnoid hemorrhage was reported among 124 patients treated with metformin while none was reported in sitagliptin arm.

Thiazolidinediones Versus DPP-4 Inhibitors

One 54-week study (NCT01183013) reported the occurrence of a cardiac outcome in one subject treated with pioglitazone (atrial fibrillation) and three subjects treated with linagliptin (one coronary artery disease, one myocardial infarction, and one tachycardia). One nervous system disorder was reported in the pioglitazone arm (peripheral nerve palsy) and one in the linagliptin arm (radiculopathy). No other cardiac disorders (acute myocardial infarction, cardiopulmonary failure, supraventricular tachycardia, congestive cardiomyopathy) were reported.

Thiazolidinediones Versus GLP-1 Agonists

One study (NCT01147627) reported one case of a nervous system disorder (facial neuritis) in the pioglitazone group (1/136). Both arms had one case of cerebral infarction. Blurred vision was reported in three participants treated with pioglitazone monotherapy and in participants treated with exenatide monotherapy.

Sulfonylureas Versus DPP-4 Inhibitors

Two short, unpublished trials tested glimepiride against DPP-4 inhibitors. One (NCT01006603) was a 52-week trial comparing glimepiride with saxagliptin, and the other (NCT01189890) was a 30-week trial comparing glimepiride to sitagliptin. Both trials had one death in the glimepiride arm while no patient died in the DPP-4 inhibitors arms. The incidences of cardiac disorders were low in both arms for both studies. The 52-week study reported three patients in glimepiride arm versus one in saxagliptin arm having heart failure, and three patients in each arm with myocardial infarction. The 30-week trial reported that 2 of 236 participants in the glimepiride arm had cardiac events (one angina unstable and one chronic cardiac failure) and 1 of 241 in the sitagliptin arm (atrial fibrillation).

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

The clinical registry study (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus glimepiride (n=307) with metformin monotherapy (n=101) at 156 weeks. It reported the occurrence of cardiac disorders in six subjects in the metformin monotherapy group (four graded as serious events), and six for the metformin plus glimepiride combination group; five graded as serious events. It also reported three serious nervous system adverse event in the metformin monotherapy arm; one subarachnoid hemorrhage, one cerebrovascular accident and one VIIth nerve paralysis, while in the combination therapy arm it reported one episode of carotid artery stenosis and one case of complicated migraine. One death was reported for the metformin monotherapy arm and six cases of fatal severe adverse events for the metformin plus glimepiride combination therapy arm. No fatal myocardial infarctions were reported in the metformin or metformin plus glimepiride arms.

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Two short-term RCTs compared the combination of metformin plus saxagliptin with metformin monotherapy. One (NCT00960076) reported the occurrence of cardiac disorders in two subjects in the metformin monotherapy group (one atherosclerotic disease and one myocardial infarction) (n=144), while none was reported for the metformin plus saxagliptin combination group (n=138). The other trial (NCT01076088) reported one subarachnoid hemorrhage in the metformin monotherapy arm (n=124) and none in the combination therapy arm (n=125). No cerebral infarction was reported for either the metformin monotherapy arm or the metformin plus saxagliptin combination therapy arm. The clinical study registry (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus sitagliptin with metformin monotherapy at 156 weeks. It reported the occurrence of cardiac disorders in six subjects in the metformin monotherapy group (four graded as serious) (n=101), and five for the metformin plus sitagliptin combination group; all graded as serious (n=302). It also reported three serious nervous system adverse event in the metformin monotherapy arm; one subarachnoid hemorrhage, one cerebrovascular accident and one VIIth nerve paralysis, while in the combination therapy arm it reported one episode of syncope. One death was reported for the metformin monotherapy arm and two cases of fatal severe adverse events for the metformin plus sitagliptin combination therapy arm.

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

The clinical study registry (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus albiglutide (n=302) with metformin monotherapy (n=101) at 156 weeks. It reported the occurrence of cardiac disorders in six subjects in the metformin monotherapy group (four graded as serious), and 14 for the metformin plus albiglutide combination group; 12 graded as serious. It also reported three serious nervous system adverse event in the metformin monotherapy arm; one subarachnoid hemorrhage, one cerebrovascular accident and one VIIth nerve paralysis, while in the combination therapy arm it reported two cases of cerebrovascular accidents, one transient ischemic attack, one case of convulsion, one of polyneuropathy and of presyncope. One death was reported for the metformin monotherapy arm and four cases of fatal severe adverse events for the metformin plus albiglutide combination therapy arm.

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

One study (NCT00856284) had 869 subjects treated with the combination of metformin plus 5 mg of glipizide, and 378 treated with the combination of metformin plus 25 mg of alogliptin. Events were reported for up to 108 weeks after initiation of study treatment. One sudden death was reported in the glipizide combination arm, but none was reported in alogliptin combination arm. Cardiac disorders were rare. The study reported coronary artery disease in three subjects in the metformin with alogliptin arm versus two subjects in the metformin with glipizide arm; one versus five for acute myocardial infarction (a statistically significant difference), three versus two with atrial fibrillation, three versus one with heart failure, none versus one with myocardial ischemia, and one in each arm with a cardiomyopathy. Cerebrovascular accident was reported in one patient in the alogliptin combination arm, and in three patients in the glipizide combination arm. Ischemic stroke (including transient ischemic attack) was reported in three patients in the alogliptin combination arm, and none in the glipizide combination arm.

The clinical study registry (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus sitagliptin with the combination of metformin plus glimepiride at 156 weeks. It reported the occurrence of cardiac disorders in six subjects in the metformin plus glimepiride group (five graded as serious) (n=307), and five for the metformin plus sitagliptin combination group; all graded as serious (n=302). It also reported two serious nervous system adverse event in the metformin plus glimepiride arm (one carotid artery stenosis and one complicated migraine), while in the metformin plus sitagliptin combination therapy arm it reported one episode of syncope. Six deaths were reported for the metformin plus glimepiride arm and two cases of fatal severe adverse events for the metformin plus sitagliptin combination therapy arm.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

The clinical study registry (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus albiglutide with the combination of metformin plus glimepiride at 156 weeks. It reported the occurrence of cardiac disorders in six subjects in the metformin plus glimepiride group (five graded as serious) (n=307), and 14 for the metformin plus albiglutide

combination group (12 graded as serious) (n=302). It also reported two serious nervous system adverse event in the metformin plus glimepiride arm (one carotid artery stenosis and one complicated migraine), while in the metformin plus albiglutide combination therapy arm it reported two cases of cerebrovascular accidents, one transient ischemic attack, one case of convulsion, one of polyneuropathy and of presyncope. Six deaths were reported for the metformin plus glimepiride arm and four deaths for the metformin plus albiglutide combination therapy arm.

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

The clinical study registry (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus albiglutide with the combination of metformin plus sitagliptin at 156 weeks. It reported the occurrence of cardiac disorders in five subjects in the metformin plus sitagliptin group (all graded as serious) (n=302), and 14 for the metformin plus albiglutide combination group (12 graded as serious) (n=302). It also reported one serious nervous system adverse event in the metformin plus sitagliptin arm (one episode of syncope), while in the metformin plus albiglutide combination therapy arm it reported two cases of cerebrovascular accidents, one transient ischemic attack, one case of convulsion, one of polyneuropathy and of presyncope. Two deaths were reported for the metformin plus sitagliptin arm and four deaths for the metformin plus albiglutide combination therapy arm.

Combination of Metformin Plus a Basal-Bolus Insulin Versus a Combination of Metformin Plus a Premixed Insulin

One study (NCT01068652) compared the effect of the combination of metformin plus basal-bolus insulin analogs (insulin detemir and aspart) with the combination of metformin plus 70/30 insulin aspart. Incidence of cardiac disorders were 2 among 200 in the metformin plus insulin detemir arm and 4 among 203 in the metformin plus biphasic insulin aspart 30 arm.

KQ3 Safety Outcomes

We found 10 unpublished reports from the ClinicalTrials.gov site that reported on safety outcomes for our comparisons of interest.

Monotherapy Comparisons

Metformin Versus DPP-4 Inhibitors

One 24-week trial (NCT01076088) compared metformin monotherapy with 100 mg of sitagliptin monotherapy. The study reported a greater incidence of GI adverse events in the metformin arm (9/124 subjects reported diarrhea and 4/124 reported nausea) than in the sitagliptin arm (2/120 for diarrhea and 0/120 for nausea). Hypoglycemia was reported in four subjects in the sitagliptin arm, and two subjects in the metformin arm.

Thiazolidinediones Versus DPP-4 Inhibitors

One trial (NCT01183013) reported no cases of diarrhea, vomiting, hypoglycemia, or acute pancreatitis in any of the 134 patients receiving pioglitazone at 45 mg daily or the 130 patients

receiving linagliptin at 5 mg daily. Cancer was reported in two patients in the pioglitazone arm and no patients in the linagliptin arm.

Thiazolidinediones Versus GLP-1 Agonists

One RCT (NCT01147627) described one patient on exenatide who developed acute pancreatitis (n=142) compared with none in the pioglitazone group (0/136). The incidence of GI disorders in the exenatide group was much higher than in the pioglitazone group (37/142 versus 1/136 for nausea, 15/142 versus 1/136 for vomiting, 6/142 versus 4/136 for diarrhea).

Sulfonylureas Versus DPP-4 Inhibitors

Two unpublished trials evaluated glimepiride against DPP-4 inhibitors. A 52-week RCT (NCT01006603) reported a much higher proportion of patients having experienced at least one hypoglycemic event (confirmed or severe) in the glimepiride group (15.3%) compared with the saxagliptin group (1.1%). Incidence of cancer was higher in the saxagliptin group (10/359) than in the glimepiride group (3/359). The incidence of GI disorders did not differ significantly among patients receiving glimepiride monotherapy and those receiving saxagliptin monotherapy (19/359 verses 15/359 for diarrhea, and 8/359 versus 4/359 for nausea).

The other trial (NCT01189890) reported symptomatic hypoglycemia up to week 30 in 11 subjects in the glimepiride monotherapy group and two subjects in the sitagliptin monotherapy group. The between-group difference in hypoglycemia incidence was -3.9% (95% CI, -7.5% to -1.2%), favoring glimepiride over sitagliptin. Three cases of cancer were reported in patients treated with sitagliptin (colon cancer, malignant melanoma, and prostate cancer), and none in those treated with glimepiride.

Metformin Versus Metformin-Based Combination Comparisons

Metformin Versus a Combination of Metformin Plus a Sulfonylurea

The clinical registry study (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus glimepiride (n=307) with metformin monotherapy (n=101) at 156 weeks. Hypoglycemia occurred in nine patients in the metformin arm and in 90 patients in the metformin plus glimepiride combination arm. None of the patients in the metformin arm had a severe hypoglycemic event, but one patient in the metformin plus glimepiride arm did. Two patients in the metformin arm (both serious) and five patients in the metformin plus glimepiride arm (four serious) had a gastrointestinal disorder. One of the gastrointestinal events in the metformin plus glimepiride arm was an acute pancreatitis. While the related publication only reported on thyroid cancer, the registry reported other types of cancer after 156 weeks; two cases of cancer in the metformin arm (breast and prostate) and seven on the combination arm (lymphoma, lung, uterus, and liver).

Metformin Versus a Combination of Metformin Plus a DPP-4 Inhibitor

Two short-term RCTs compared the combination of metformin plus saxagliptin with metformin monotherapy. One trial (NCT00960076) reported diarrhea in five out of 144 patients in the metformin monotherapy group (3.5%), which was comparable to the incidence among patients treated with saxagliptin as add-on therapy to metformin (8/138, 5.8%). The other trial (NCT01076088) reported a similar incidence of GI adverse events in both the metformin monotherapy group (nine people reported diarrhea and four reported nausea) and the metformin

plus sitagliptin combination group (four for diarrhea and eight for nausea). Hypoglycemia events did not differ significantly among patients treated with combination therapy (7/125) and patients treated with metformin monotherapy (2/124).

The clinical study registry (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus sitagliptin (n=302) with metformin monotherapy (n=101) at 156 weeks. Hypoglycemia occurred in nine patients in the metformin arm and in 16 patients in the metformin plus sitagliptin combination arm. None of the hypoglycemic events were severe. Two patients in the metformin arm and one patient in the metformin plus sitagliptin arm had a serious gastrointestinal disorder. The registry did not record any cases of acute pancreatitis among the patients in the metformin and in the metformin plus sitagliptin arms. The registry reported two cases of cancer in the metformin arm (breast and prostate) and ten on the combination arm (two cases of thyroid cancer and eight other cases; breast, prostate, lung, renal, and gastrointestinal).

Metformin Versus a Combination of Metformin Plus a GLP-1 Agonist

The clinical study registry (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus albiglutide (n=302) with metformin monotherapy (n=101) at 156 weeks. Hypoglycemia occurred in nine patients in the metformin arm and in 28 patients in the metformin plus albiglutide combination arm. None of the hypoglycemic events were severe. Two patients in the metformin arm and six patients in the metformin plus albiglutide arm had a serious gastrointestinal disorder. One of the serious gastrointestinal events in the metformin plus albiglutide arms was an acute pancreatitis. The registry reported two cases of cancer in the metformin arm (breast and prostate) and three in the combination arm (thyroid, uterus, and bladder).

Metformin-Based Combination Comparisons

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a DPP-4 Inhibitor

One study (NCT00856284) with up to 104 weeks of followup had 869 subjects treated with the combination of metformin plus glipizide 5 mg, and 378 treated with the combination of metformin plus alogliptin at 25 mg daily. Hypoglycemia was rare and did not differ between arms. The metformin plus glipizide combination therapy arm reported had the only participant developing pancreatitis. The occurrence of GI adverse events was more frequently among patients receiving metformin plus alogliptin combination therapy (32 nausea, 1 severe vomiting, 60 diarrhea) than metformin plus glipizide combination therapy (20 nausea and 63 diarrhea), but this was not statistically significant. No severe diarrhea was reported in either group. Two cases of cancer were reported in the glipizide combination group (breast cancer and endometrial cancer), while three were reported in the alogliptin combination group (colon cancer and ovarian cancer).

The clinical study registry (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus sitagliptin (n=302) with the combination of metformin plus glimepiride (n=307) at 156 weeks. Hypoglycemia occurred in 90 patients in the metformin plus glimepiride combination arm and in 16 patients in the metformin plus sitagliptin combination arm. None of the patients in the metformin plus sitagliptin arm had a severe hypoglycemic event, but one patient in the metformin plus glimepiride arm did. Two patients in the metformin arm (both serious) and five patients in the metformin plus glimepiride arm (four serious) had a

gastrointestinal disorder. One of the gastrointestinal events in the metformin plus glimepiride arm was an acute pancreatitis, and no pancreatitis was reported in the metformin plus DPP-4 inhibitor arm. While the related publication only reported on thyroid cancer, the registry reported other types of cancer after 156 weeks; seven cases in the metformin plus glimepiride combination arm (lymphoma, lung, uterus, and liver) and ten in the metformin plus sitagliptin combination arm (two cases of thyroid cancer and eight other cases; breast, prostate, lung, renal, and gastrointestinal).

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a SGLT-2 Inhibitor

One 52-week trial in Japan (NCT01368081) evaluated several safety outcomes for the combination of metformin plus sulfonylurea relative to the combination of metformin plus empagliflozin. Five out of 63 participants in the metformin plus sulfonylurea combination group experienced confirmed hypoglycemic events, which did not differ from the incidence in the metformin plus empagliflozin combination group (1 out of 65 participants). Five diarrhea cases were reported in metformin plus sulfonylurea arm, compared with four in the metformin plus empagliflozin arm. No drug-induced liver injury, no urinary tract infection, and no fractures were seen in either arm.

Combination of Metformin Plus a Sulfonylurea Versus a Combination of Metformin Plus a GLP-1 Agonist

The clinical study registry (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus albiglutide (n=302) with the combination of metformin plus glimepiride (n=307) at 156 weeks. Hypoglycemia occurred in 90 patients in the metformin plus glimepiride combination arm and in 28 patients in the metformin plus albiglutide combination arm. None of the patients in the metformin plus albiglutide arm had a severe hypoglycemic event, but one patient in the metformin plus glimepiride arm did. Five patients in the metformin plus glimepiride arm (four serious) and seven patients (six serious) in the metformin plus albiglutide arm had a gastrointestinal disorder. One of the gastrointestinal events in each arm was an acute pancreatitis. While the related publication only reported on thyroid cancer, the registry reported other types of cancer after 156 weeks; seven cases in the metformin plus glimepiride combination arm (lymphoma, lung, uterus, and liver) and three in the metformin plus albiglutide combination arm (thyroid, uterus, and bladder).

Combination of Metformin Plus a DPP-4 Inhibitor Versus a Combination of Metformin Plus a GLP-1 Agonist

The clinical study registry (NCT00838903-Glaxo study GLP112753) compared the combination of metformin plus albiglutide (n=302) with the combination of metformin plus sitagliptin (n=302) at 156 weeks. Hypoglycemia occurred in 16 patients in the metformin plus sitagliptin combination arm and in 28 patients in the metformin plus albiglutide combination arm. None of the events were considered serious. Two patients in the metformin plus sitagliptin arm (two serious) and seven patients (six serious) in the metformin plus albiglutide arm had a gastrointestinal disorder. One of the gastrointestinal events in the metformin plus albiglutide arm was an acute pancreatitis, and no cases of acute pancreatitis were reported in the metformin plus DPP-4 inhibitor arm. While the related publication only reported on thyroid cancer, the registry reported other types of cancer after 156 weeks; ten in the metformin plus sitagliptin combination

arm (two cases of thyroid cancer and eight other cases; breast, prostate, lung, renal, and gastrointestinal) and three in the metformin plus albiglutide combination arm (thyroid, uterus, and bladder).

Combination of Metformin Plus a Basal Insulin Versus a Combination of Metformin Plus a Premixed Insulin

One study (NCT01068652) had 200 subjects in the metformin plus insulin detemir combination therapy group and 203 in the metformin plus biphasic insulin aspart 30 combination therapy group. One cancer case was reported in subjects treated with combination of metformin plus insulin detemir (breast cancer) but none in the comparison group. Diarrhea was reported in 13 subjects in the metformin plus insulin detemir combination group, and 15 in the metformin plus biphasic insulin aspart 30 combination group.

Articles Reporting More Than One Study

Sixteen studies reported on more than one study (see Table E1).[236-251] Since many of these studies pooled data from studies already included in our review, we did not abstract that data. For articles that pooled data from studies not included in our review, we abstracted and reported the results. The results from these studies are consistent with the findings from our review.

Table E1. Summary of studies reporting on more than one study

Author, year	Results of pooled studies if not duplicated or already in our report
Del Prato, 2013[243]	Individual studies were included in the report
Sjostrand, 2014[244]	Individual studies were included in the report
Davidson, 2014[245]	Individual studies were included in the report
Grimm, 2013[246]	Individual studies were included in the report
Rosenstock, 2013[247]	Individual studies were included in the report
Karyekar, 2011[248]	Individual studies were included in the report
Home, 2010[249]	Individual studies were included in the report
Jendle, 2009[250]	Individual studies were included in the report
Belcher, 2004[236]	Mean blood pressure was slightly reduced by all treatments, with pioglitazone treatment resulting in the largest falls (approximately 1.5 mmHg). Hospitalizations for cardiac or cerebrovascular events were similar with the different treatments. Overall mortality was 7 of 1857 for pioglitazone and 10 of 1856 for non-pioglitazone treatments, of which 3 and 6 were cardiac deaths, respectively. The incidence of congestive cardiac failure was similar with pioglitazone (12/1857) and non-pioglitazone (10/1856) treatments.
Lester, 2005[237]	Individual studies were included in the report
Belcher, 2005[238]	Individual studies were included in the report
Belcher, 2005[239]	Individual studies were included in the report
Charbonnel, 2005[240]	Individual studies were included in the report
Ceriello, 2005[241]	Individual studies were included in the report
Rendell, 2003[242]	Individual studies were included in the report
Bailey, 2015[251]	Individual studies were included in the report

mmHg = millimeters of mercury; HR =hazard ratio; CI =confidence interval; mmol/L = millimoles per liter

Appendix F. Key Points and Evidence Grades

Key Points and Evidence Grades for Intermediate Outcomes

- Conclusions for all the intermediate outcomes are short term (≤ 1 year) due to the few studies of longer duration evaluating these outcomes.
- Of the few studies that did evaluate longer time frames (≥2 years), almost all had at least 20 percent losses to followup, making it challenging to draw firm conclusions about long term outcomes.

Hemoglobin A1c

Monotherapy Comparisons

- Most oral diabetes medications had similar efficacy in achieving reductions in hemoglobin A1c (HbA1c).

o In the prior report, the strength of evidence was graded as high that metformin was similar to sulfonylurea (pooled between-group difference of 0.1%; 95% confidence interval [CI], -0.1% to 0.3%).Therefore, we did not update this comparison for HbA1c in this review.

  - o The strength of evidence (SOE) was graded as high that metformin was similar to thiazolidinedione (pooled between-group difference of -0.04%; 95% CI, -0.11% to 0.03%).
  - o Thiazolidinediones performed similarly to sulfonylureas (pooled between-group difference of -0.04%; 95% CI, -0.13% to 0.06%). (SOE: High)
  - o The SOE was graded as low or insufficient for the monotherapy comparisons with the newer classes of sodium-glucose cotransporter (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, and will warrant further study.

- The one exception was that metformin had a greater reduction in HbA1c compared with dipeptidyl peptidase-4 (DPP-4) inhibitors (pooled between-group difference of -0.4%; 95% CI, -0.5% to -0.3%). (SOE: High)

Metformin-Based Combination Comparisons

- The combination of metformin plus GLP-1 agonists reduced HbA1c more than metformin plus DPP-4 inhibitors, with a pooled between-group difference of -0.65% (95% CI, -0.75% to -0.54%) in the short-term. (SOE: Moderate)
- Most other combination therapy comparisons had either no significant or no clinically meaningful (<0.3%) between-group differences in HbA1c between arms.
- The evidence was graded as moderate for the following comparisons: metformin plus a thiazolidinedione versus metformin plus a sulfonylurea, metformin plus a thiazolidinedione versus metformin plus a DPP-4 inhibitor, metformin plus a sulfonylurea versus metformin plus an SGLT-2 inhibitor, metformin plus a DPP-4 inhibitor versus metformin plus an SGLT-2 inhibitor, and metformin plus a DPP-4 inhibitor versus metformin plus a GLP-1 agonist.
- Despite the clinical interest in comparing metformin plus injectables, there was insufficient or low strength of evidence on glycemic control for the following

comparisons: metformin plus the GLP-1 agonists versus metformin plus basal or premixed insulin, and metformin plus premixed insulin versus metformin plus basal insulin.

Weight

Monotherapy Comparisons

- In the 2011 report, metformin had greater weight reduction than thiazolidinediones (pooled mean between-group difference of -2.6 kg; 95% CI, -4.1 kg to -1.2 kg) or sulfonylureas (pooled mean between-group difference of -2.7 kg; 95% CI, -3.5 kg to -1.9 kg) with high strength of evidence. Therefore, we did not update these two comparisons in this report.
- Metformin had greater weight reduction than DPP-4 inhibitors (pooled mean between-group difference, -1.3 kg; 95% CI, -1.6 kg to -1.0 kg). (SOE: High)
- SGLT-2 inhibitors had greater weight reduction when compared with metformin or DPP-4 inhibitors (between-group differences ranging from -1.3 kg to -2.7 kg). (SOE: Moderate for both comparisons)
- DPP-4 inhibitors and GLP-1 agonists both decreased weight more than thiazolidinediones (between-group differences ranging from -2.3 kg to -3.5 kg). (SOE: Moderate for both comparisons)
- GLP-1 agonists decreased weight more than sulfonylureas (pooled mean between-group difference, -2.3 kg; 95% CI, -3.3 kg to -1.2 kg). (SOE: Moderate)
- Sulfonylureas caused slightly less weight gain when compared with thiazolidinediones (between-group difference of -1.2 kg; 95% CI, -1.8 kg to -0.6 kg). (SOE: Moderate)

Metformin Versus Metformin-Based Combination Comparisons

- Metformin monotherapy reduced weight more than the combination of metformin plus a thiazolidinedione (pooled mean between-group difference, -2.2 kg; 95% CI, -2.6 kg to -1.9 kg) or metformin plus a sulfonylurea (pooled mean between-group difference, -2.2 kg, 95% CI, -3.4 kg to -1.0 kg). (SOE: High for both comparisons)
- When compared with metformin monotherapy, the combination of metformin plus
  - SGLT-2 inhibitor had greater weight reduction (pooled mean between-group difference, -2.0 kg; 95% CI, -2.5 kg to -1.5 kg). (SOE: High)
  - GLP-1 agonist had greater weight reduction (pooled mean between-group difference, -2.0 kg; 95% CI, -2.7 kg to -1.3 kg). (SOE: Moderate)
- Metformin monotherapy had no significant differences in weight when compared with the combination of metformin plus DPP-4 inhibitors (pooled mean between-group difference, -0.1 kg; 95% CI, -0.2 kg to 0.03 kg). (SOE: Moderate)

Metformin-Based Combination Comparisons

- The combinations of metformin plus a sulfonylurea, metformin plus a GLP-1 agonist, and metformin plus a DPP-4 inhibitor all had a more favorable effect on weight compared with metformin plus a thiazolidinedione (range in between-group differences, -0.9 kg to -5.1 kg). (SOE: Moderate for all comparisons)

- When compared with the combination of metformin plus a sulfonylurea, the combination of metformin plus
  - DPP-4 inhibitors had more favorable effects on weight (pooled mean between-group difference, -2.2 kg; 95% CI, -1.8 kg to -2.5 kg). (SOE: High)
  - SGLT-2 inhibitors had more favorable effects on weight (pooled mean between-group difference, -4.7 kg; 95% CI, -4.4 kg to -5.0 kg). (SOE: High)
  - GLP-1 agonist had more favorable effects on weight (range in mean between-group differences, -2.4 kg to -12.3 kg). (SOE: Moderate)
  - Premixed insulin or basal insulin had **less** favorable effects on weight (range in mean between-group differences, 0.5 kg to 1.7 kg). The strength of evidence was low for both comparisons, due to the small number of studies. However, taken together, the strength of evidence would be moderate favoring metformin plus sulfonylurea over metformin plus a premixed or long-acting insulin.
- When compared with metformin plus a DPP-4 inhibitor, the combination of metformin plus
  - GLP-1 agonist had greater reductions in weight (pooled mean between-group difference, -1.8 kg; 95% CI, -1.1 kg to -2.5 kg). (SOE: Moderate)
  - SGLT-2 inhibitors had greater reductions in weight (between-group differences of around -2.5 kg). (SOE: Moderate)
- Despite the clinical interest in comparing metformin plus injectables, there was low strength of evidence on weight for the following comparisons: metformin plus the GLP-1 agonists versus metformin plus basal or premixed insulin, and metformin plus premixed insulin versus metformin plus basal insulin.

Systolic Blood Pressure (for Comparisons That Include SGLT-2 Inhibitors or GLP-1 Agonists)

Monotherapy Comparisons

- SGLT-2 inhibitors had a greater reduction in systolic blood pressure compared with metformin, (pooled between-group difference of -2.8 mmHg; 95% CI, -2.6 mmHg to -3.0 mmHg). (SOE: Moderate)
- The strength of evidence was graded low or insufficient for the following comparisons:
  - SGLT-2 inhibitors versus DPP-4 inhibitors, and
  - GLP-1 agonists versus metformin, thiazolidinediones, sulfonylureas, and DPP-4 inhibitors.

Metformin Versus Metformin-Based Combination Comparisons

- Metformin plus a SGLT-2 inhibitor reduced systolic blood pressure more than metformin alone (pooled between-group difference of -4.4 mmHg; 95% CI, -2.9 to -6.0 mmHg) for shorter studies. (SOE: High)
- Metformin plus a GLP-1 agonist reduced systolic blood pressure more than metformin alone (pooled between-group difference of -3.1 mmHg; 95% CI, -1.4 to -4.9 mmHg). (SOE: Moderate)

Metformin-Based Combination Comparisons

- Metformin plus a SGLT-2 inhibitor reduced systolic blood pressure more than metformin plus a sulfonylurea (pooled between-group difference, -5.0 mmHg; 95% CI, -4.2 mmHg to -6.0 mmHg) or metformin plus a DPP-4 inhibitor (pooled between-group difference, -4.1 mmHg; 95% CI, -3.6 mmHg to -4.6 mmHg). (SOE: High and Moderate, respectively)

Heart Rate (for Comparisons That Include SGLT-2 Inhibitors or GLP-1 Agonists)

Monotherapy Comparisons

- Metformin compared with a GLP-1 agonist yielded no differences in heart rate between arms. (SOE: Moderate)

Metformin Versus Metformin-Based Combination Comparisons

- There was low or insufficient evidence for all metformin combination therapies compared with metformin alone.

Metformin-Based Combination Comparisons

Combination therapy with metformin plus a SGLT-2 inhibitor resulted in less increase in heart rate compared with metformin plus a sulfonylurea (pooled between group difference in heart rate, -1.5 bpm; 95% CI, -0.6 bpm to -2.3 bpm). (SOE: Moderate)

Key Points and Evidence Grades for Long-Term Outcomes

All-Cause Mortality

- All evidence on all-cause mortality was of low strength or insufficient

Cardiovascular Mortality

- Sulfonylurea monotherapy was associated with increased cardiovascular mortality compared with metformin monotherapy (relative risk range 1.5 to 1.7 from individual RCTs; range in risk differences, 0.1 to 2.9%; range in duration of follow up, 2.8 to 4.0 years). (SOE: Moderate)
- To date, there has been uncertainty about the cardiovascular benefits of diabetes medications as evidenced by the FDA labeling stating a lack of known lower macrovascular risk for any diabetes medications; still, all evidence on the comparative effectiveness of the included diabetes medications on cardiovascular mortality was of low strength or insufficient.

Cardiovascular and Cerebrovascular Disease Morbidity

- To date, there has been uncertainty about the cardiovascular benefits of diabetes medications as evidenced by the FDA labeling stating a lack of known lower macrovascular risk for any diabetes medications; still, all evidence on the comparative effectiveness of the included diabetes medications on cardiovascular mobidity was of low strength or insufficient.

Retinopathy, Nephropathy, and Neuropathy

- The evidence was low or insufficient for all comparisons, and almost all RCTs were short-term.

Key Points and Evidence Grades for Safety

Hypoglycemia

Mild, Moderate, or Total Hypoglycemia

Unless otherwise noted, results on hypoglycemia refer to the number of participants experiencing hypoglycemia and not to the number of events.

- Metformin monotherapy was favored over the following:
  - Sulfonylurea monotherapy for mild-moderate hypoglycemia (pooled OR for sulfonylurea versus metformin, 4.00; 95% CI, 1.75 to 9.83) (SOE: High);
  - The combination of metformin plus a thiazolidinedione (pooled OR for metformin plus a thiazolidinedione versus metformin monotherapy for total hypoglycemia, 1.56; 95% CI, 0.99 to 2.44) (SOE: Moderate);
  - The combination of metformin plus a sulfonylurea for mild, moderate, or total hypoglycemia (range in ORs, 2.15 to 28.6) (SOE: Moderate).
  - The combination of metformin plus an SGLT-2 inhibitor for mild or moderate hypoglycemia (pooled OR, 1.74; 95% CI, 0.83 to 3.66) (SOE: Moderate).
- The risks of mild-moderate and total hypoglycemia were similar for metformin monotherapy and the combination of metformin plus a DPP-4 inhibitor. (SOE: High)
  - Pooled OR for metformin plus a DPP-4 inhibitor versus metformin monotherapy:
    - Mild-moderate hypoglycemia: 0.97; 95% CI, 0.63 to 1.51
    - Total hypoglycemia: 0.92; 95% CI, 0.43 to 1.97
- Sulfonylurea monotherapy increased the risk of total hypoglycemia compared with thiazolidinedione monotherapy (pooled OR 6.31; 95% CI, 4.08 to 9.76). (SOE: High)
- SGLT-2 inhibitor monotherapy was associated with a lower risk of hypoglycemia compared with metformin monotherapy (pooled OR, 0.46; 95% CI, 0.16 to 1.30). (SOE: Moderate)
- DPP-4 inhibitor monotherapy was favored over sulfonylurea monotherapy (range of OR, 0.08 to 0.26 from individual studies for sulfonylurea versus DPP-4 inhibitor monotherapy). (SOE: Moderate)
- Mild-moderate hypoglycemia was more common with sulfonylurea monotherapy than with GLP-1 agonist monotherapy (range in OR, 3.2 to 5.3). (SOE: Moderate)
- When compared with metformin plus a sulfonylurea, metformin plus an SGLT-2 inhibitor had less risk of mild or moderate hypoglycemia (range in OR, 0.03 to 0.13). (SOE: High)
- When compared with metformin plus sulfonylurea, several combinations had less risk of mild, moderate, or total hypoglycemia: metformin plus a thiazolidinedione, metformin plus a DPP-4 inhibitor, and metformin plus a GLP-1 agonist (range in OR, 0.07 to 0.27). (SOE: High or Moderate for all comparisons)
- When compared with metformin plus basal insulin or premixed insulin, metformin plus a GLP-1 agonist had less risk of mild or moderate hypoglycemia (range in OR, 0.18 to 0.35). (SOE: Moderate)

- Moderate grade evidence showed a lower risk of hypoglycemia when metformin is combined with a basal insulin rather than a premixed insulin (range in OR, 0.23 to 0.89).

Severe Hypoglycemia

- Only the sulfonylurea comparisons convincingly demonstrated an increased risk of severe hypoglycemia in the sulfonylurea arms compared with nonsulfonylurea medications:
  - Sulfonylurea versus metformin (range in OR, 1.41 to 2.04) (SOE: Moderate)
  - Sulfonylurea versus thiazolidinediones (OR, 8.1) (SOE: Moderate)
  - Metformin plus sulfonylurea versus metformin plus SGLT-2 inhibitors, and metformin plus sulfonylurea versus metformin plus DPP-4 inhibitors. (SOE: Moderate or High)
- Only two comparisons had sufficient evidence to show no between-group differences in severe hypoglycemia: the combination of metformin plus thiazolidinediones versus metformin plus DPP-4 inhibitors and metformin monotherapy versus metformin plus a DPP-4 inhibitor. (SOE: Moderate)

Gastrointestinal (GI) Side Effects

- GI adverse events are more common with:
  - metformin than with DPP-4 inhibitors (pooled OR 2.6 and 2.7 for diarrhea and nausea, favoring DPP-4 inhibitors), (SOE: High);
  - metformin than thiazolidinediones (between 1.7 to 4.2 fold higher risk), (SOE: Moderate);
  - metformin than sulfonylureas (between 2.2 to 2.4 fold higher risk), (SOE: Moderate);
  - GLP-1 agonists than metformin for nausea and vomiting (between 1.3 to 1.7 fold increased risk with GLP-1 agonists). (SOE: Moderate)
  - GLP-1 agonists than sulfonylureas (between 1.5 to 2.4 fold higher risk of diarrhea), (SOE: Moderate)
  - metformin plus a GLP-1 agonist than metformin plus a DPP-4 inhibitor (between 1.0 to 7.8 fold higher risk with metformin plus GLP-1 agonists), (SOE: Moderate);
  - metformin plus a GLP-1 agonist than metformin plus a thiazolidinedione (between 2.9 to 6.3 fold higher risk with metformin plus a GLP-1 agonist). (SOE: Moderate)
- GI adverse events are equally common with:
  - thiazolidinediones and sulfonylureas, (SOE: High);
  - metformin monotherapy and metformin plus a DPP-4 inhibitor, (SOE: Moderate for any GI adverse event, nausea, and vomiting for shorter duration studies);
  - metformin plus a sulfonylurea and metformin plus a DPP-4 inhibitor in longer studies, (SOE: High);
  - metformin monotherapy and combination therapy with metformin plus a SGLT-2 inhibitor (for diarrhea), (SOE: Moderate);
    - metformin plus a thiazolidinedione and metformin plus a sulfonylurea. (SOE: Moderate)

Cancer

- Type of cancer was not designated *a priori* in most of the studies reporting on cancer; thus, the following conclusions apply to any cancer, unless specified.

- Even though the FDA has issued warnings regarding increased risk of bladder cancer risk with pioglitazone, we found low or insufficient strength of evidence on TZD-based comparisons and cancer outcomes.
- Despite FDA warnings of a possible increased risk of thyroid cancer with GLP-1 agonists, we found low-strength or insufficient evidence on GLP-1 agonist-based comparisons and cancer outcomes.

Congestive Heart Failure

- Thiazolidinediones alone increase the risk of heart failure when compared with sulfonylureas (pooled OR in four RCTs of 1.6; 95% CI, 0.96 to 2.8) or metformin (two short RCTs with no events, one 4-year RCT with an absolute risk difference of 3% and range in HR of 1.2 to 1.5 in two observational studies). (SOE: Low)
- Despite recent concerns of congestive heart failure with DPP-4 inhibitors, we found low or insufficient strength of evidence on the comparative safety of this drug class for this outcome.

Pancreatitis

- Despite FDA warnings regarding an increased risk of pancreatitis with GLP-1 agonists and DPP-4 inhibitors, we found low or insufficient evidence on the comparative safety of these drug classes for this outcome.

Genital Mycotic Infections (for Comparisons That Include SGLT-2 Inhibitors)

- Compared to metformin monotherapy, genital infection rates were higher for SGLT-2 inhibitor monotherapy and for the combination of metformin plus an SGLT-2 inhibitor Rates of genital infections for combination therapy with metformin plus an SGLT-2 inhibitor were higher compared to the following**:**
  - Metformin monotherapy: pooled OR for women, 3.0; 95% CI, 1.2 to 7.2 and pooled OR for men, 2.7; 95% CI, 0.8 to 9.0 (SOE: High)
  - Metformin plus a sulfonylurea: pooled OR for women, 5.2; 95% CI, 3.4 to 7.8; pooled OR for men, 7.6; 95% CI, 4.0 to 14.4 (SOE: High)
  - Metformin plus a DPP-4 inhibitor

Other Serious Adverse Events

- There was no moderate or high strength of evidence for the following adverse events: liver injury, lactic acidosis, severe allergic reactions, macular edema/decreased vision, urinary tract infections (for SGLT-2 inhibitors) impaired renal function (for SGLT-2 inhibitors), fractures (for SGLT-2 inhibitors), and volume depletion (for SGLT-2 inhibitors). Therefore, we were unable to draw any firm conclusions regarding the diabetes medication comparisons and these safety outcomes.
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Key Question 4: Subgroups

- Although thirty-two studies reported on the comparative effectiveness and safety for sub-populations relevant to Key Question 4 (Appendix D, Table D14), few studies had

sufficient power to assess comparative effectiveness or safety by subgroup. The evidence favoring one medication over another across subgroups is unclear.

Appendix G. References

1. Aaboe K, Knop FK, Vilsboll T, et al. Twelve weeks treatment with the DPP-4 inhibitor, sitagliptin, prevents degradation of peptide YY and improves glucose and non-glucose induced insulin secretion in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2010 Apr;12(4):323-33. PMID: 20380653.
2. Ahren B, Johnson SL, Stewart M, et al. HARMONY 3: 104-Week Randomized, Double-Blind, Placebo- and Active-Controlled Trial Assessing the Efficacy and Safety of Albiglutide Compared With Placebo, Sitagliptin, and Glimepiride in Patients With Type 2 Diabetes Taking Metformin. Diabetes Care. 2014 Jun 4PMID: 24898304.
3. Alba M, Ahren B, Inzucchi SE, et al. Sitagliptin and pioglitazone provide complementary effects on postprandial glucose and pancreatic islet cell function. Diabetes Obes Metab. 2013 Dec;15(12):1101-10. PMID: 23782502.
4. Apovian CM, Bergenstal RM, Cuddihy RM, et al. Effects of exenatide combined with lifestyle modification in patients with type 2 diabetes. Am J Med. 2010 May;123(5):468 e9-17. PMID: 20399326.
5. Arechavaleta R, Seck T, Chen Y, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2011 Feb;13(2):160-8. PMID: 21199268.
6. Arjona Ferreira JC, Marre M, Barzilai N, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. Diabetes Care. 2013 May;36(5):1067-73. PMID: 23248197.
7. Aschner P, Katzeff HL, Guo H, et al. Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. Diabetes Obes Metab. 2010 Mar;12(3):252-61. PMID: 20070351.
8. Aschner P, Chan J, Owens DR, et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. Lancet. 2012 Jun 16;379(9833):2262-9. PMID: 22683131.
9. Bailey CJ, Bagdonas A, Rubes J, et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. Clin Ther. 2005 2005 Oct;27(10):1548-61.
10. Bailey CJ, Gross JL, Hennicken D, et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013;11:43. PMID: 23425012.
11. Bakris G, Viberti G, Weston WM, et al. Rosiglitazone reduces urinary albumin excretion in type II diabetes. J Hum Hypertens. 2003 2003 Jan;17(1):7-12.
12. Bakris GL, Ruilope LM, McMorn SO, et al. Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria. J Hypertens. 2006 2006 Oct;24(10):2047-55.
13. Barnett AH, Patel S, Harper R, et al. Linagliptin monotherapy in type 2 diabetes patients for whom metformin is inappropriate: an 18-week randomized, double-blind, placebo-controlled phase III trial with a 34-week active-controlled extension. Diabetes Obes Metab. 2012 Dec;14(12):1145-54. PMID: 22974280.
14. Bergenstal RM, Wysham C, Macconell L, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet. 2010 Aug 7;376(9739):431-9. PMID: 20580422.
15. Bergenstal RM, Forti A, Chiasson JL, et al. Efficacy and safety of taspoglutide versus sitagliptin for type 2 diabetes mellitus (T-emerge 4 trial). Diabetes Ther. 2012 Dec;3(1):13. PMID: 23138449.
16. Blonde L, Rosenstock J, Mooradian AD, et al. Glyburide/metformin combination product is safe and efficacious in patients with type 2 diabetes failing sulphonylurea therapy. Diabetes Obes Metab. 2002 2002 Nov;4(6):368-75.
17. Bolinder J, Ljunggren O, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab. 2012 Mar;97(3):1020-31. PMID: 22238392.
18. Borges JL, Bilezikian JP, Jones-Leone AR, et al. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naive type 2 diabetes mellitus patients. Diabetes Obes Metab. 2011 Nov;13(11):1036-46. PMID: 21682834.
19. Campbell IW, Menzies DG, Chalmers J, et al. One year comparative trial of metformin and glipizide in type 2 diabetes mellitus. Diabete Metab. 1994 1994 Jul-Aug;20(4):394-400.
20. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013 Sep 14;382(9896):941-50. PMID: 23850055.
21. Charbonnel B, Karasik A, Liu J, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care. 2006 2006 Dec;29(12):2638-43.
22. Charpentier G, Fleury F, Kabir M, et al. Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. Diabet Med. 2001 2001 Oct;18(10):828-34.
23. Chawla S, Kaushik N, Singh NP, et al. Effect of addition of either sitagliptin or pioglitazone in patients with uncontrolled type 2 diabetes mellitus on metformin: A randomized controlled trial. J Pharmacol Pharmacother. 2013 Jan;4(1):27-32. PMID: 23662021.
24. Chien HH, Chang CT, Chu NF, et al. Effect of glyburide-metformin combination tablet in patients with type 2 diabetes. J Chin Med Assoc. 2007 2007 Nov;70(11):473-80.

25. Comaschi M, Demicheli A, Di Pietro C, et al. Effects of pioglitazone in combination with metformin or a sulfonylurea compared to a fixed-dose combination of metformin and glibenclamide in patients with type 2 diabetes. Diabetes Technol Ther. 2007 2007 Aug;9(4):387-98.
26. Davies MJ, Thaware PK, Tringham JR, et al. A randomized controlled trial examining combinations of repaglinide, metformin and NPH insulin. Diabet Med. 2007 2007 Jul;24(7):714-9.
27. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995 1995 Aug 31;333(9):541-9.
28. DeFronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005 May;28(5):1092-100. PMID: 15855572.
29. DeFronzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care. 2009 Sep;32(9):1649-55. PMID: 19478198.
30. DeFronzo RA, Triplitt C, Qu Y, et al. Effects of exenatide plus rosiglitazone on beta-cell function and insulin sensitivity in subjects with type 2 diabetes on metformin. Diabetes Care. 2010 May;33(5):951-7. PMID: 20107105.
31. DeFronzo RA, Burant CF, Fleck P, et al. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. J Clin Endocrinol Metab. 2012 May;97(5):1615-22. PMID: 22419732.
32. Del Prato S, Nauck M, Duran-Garcia S, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in type 2 diabetes patients: 4-year data. Diabetes Obes Metab. 2015 Mar 4PMID: 25735400.
33. Del Prato S, Camisasca R, Wilson C, et al. Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study. Diabetes Obes Metab. 2014 Dec;16(12):1239-46. PMID: 25132212.
34. Derosa G, Franzetti I, Gadaleta G, et al. Metabolic variations with oral antidiabetic drugs in patients with Type 2 diabetes: comparison between glimepiride and metformin. Diabetes Nutr Metab. 2004 2004 Jun;17(3):143-50.
35. Derosa G, Cicero AF, Gaddi AV, et al. Long-term effects of glimepiride or rosiglitazone in combination with metformin on blood pressure control in type 2 diabetic patients affected by the metabolic syndrome: a 12-month, double-blind, randomized clinical trial. Clin Ther. 2005 2005 Sep;27(9):1383-91.
36. Derosa G, Gaddi AV, Piccinni MN, et al. Antithrombotic effects of rosiglitazone-metformin versus glimepiride-metformin combination therapy in patients with type 2 diabetes mellitus and metabolic syndrome. Pharmacotherapy. 2005 2005 May;25(5):637-45.
37. Derosa G, Gaddi AV, Ciccarelli L, et al. Long-term effect of glimepiride and rosiglitazone on non-conventional cardiovascular risk factors in metformin-treated patients affected by metabolic syndrome: a randomized, double-blind clinical trial. J Int Med Res. 2005 2005 May-Jun;33(3):284-94.
38. Derosa G, Maffioli P, Salvadeo SA, et al. Direct comparison among oral hypoglycemic agents and their association with insulin resistance evaluated by euglycemic hyperinsulinemic clamp: the 60's study. Metabolism. 2009 2009 Apr 22.
39. Derosa G, Maffioli P, Salvadeo SA, et al. Exenatide versus glibenclamide in patients with diabetes. Diabetes Technol Ther. 2010 Mar;12(3):233-40. PMID: 20151774.
40. Derosa G, Putignano P, Bossi AC, et al. Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type 2 diabetic patients. Eur J Pharmacol. 2011 Sep;666(1-3):251-6. PMID: 21645507.
41. Derosa G, Carbone A, D'Angelo A, et al. A randomized, double-blind, placebo-controlled trial evaluating sitagliptin action on insulin resistance parameters and beta-cell function. Expert Opin Pharmacother. 2012 Dec;13(17):2433-42. PMID: 23061989.
42. Derosa G, Carbone A, D'Angelo A, et al. Variations in inflammatory biomarkers following the addition of sitagliptin in patients with type 2 diabetes not controlled with metformin. Intern Med. 2013;52(19):2179-87. PMID: 24088749.
43. Derosa G, Cicero AF, Franzetti IG, et al. Effects of exenatide and metformin in combination on some adipocytokine levels: a comparison with metformin monotherapy. Can J Physiol Pharmacol. 2013 Sep;91(9):724-32. PMID: 23984793.
44. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet. 2010 Jun 26;375(9733):2234-43. PMID: 20609969.
45. Einhorn D, Rendell M, Rosenzweig J, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The Pioglitazone 027 Study Group. Clin Ther. 2000 2000 Dec;22(12):1395-409.
46. Erdem G, Dogru T, Tasci I, et al. The effects of pioglitazone and metformin on plasma visfatin levels in patients with treatment naive type 2 diabetes mellitus. Diabetes Res Clin Pract. 2008 2008 Nov;82(2):214-8.
47. Erem C, Ozbas HM, Nuhoglu I, et al. Comparison of effects of gliclazide, metformin and pioglitazone monotherapies on glycemic control and cardiovascular risk factors in patients with newly diagnosed uncontrolled type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2014 May;122(5):295-302. PMID: 24710641.
48. Esposito K, Maiorino MI, Di Palo C, et al. Effects of pioglitazone versus metformin on circulating endothelial microparticles and progenitor cells in patients with newly diagnosed type 2 diabetes--a randomized controlled trial. Diabetes Obes Metab. 2011 May;13(5):439-45. PMID: 21255215.
49. Esteghamati A, Ghasemiesfe M, Mousavizadeh M, et al. Pioglitazone and metformin are equally effective in reduction of chemerin in patients with type 2 diabetes. J Diabetes Investig. 2014 May 4;5(3):327-32. PMID: 24843782.

50. Esteghamati A, Azizi R, Ebadi M, et al. The Comparative Effect of Pioglitazone and Metformin on Serum Osteoprotegerin, Adiponectin and Intercellular Adhesion Molecule Concentrations in Patients with Newly Diagnosed Type 2 Diabetes: a Randomized Clinical Trial. Exp Clin Endocrinol Diabetes. 2015 Jan 21PMID: 25607338.
51. Farcasiu E, Ivanyi T, Mozejko-Pastewka B, et al. Efficacy and safety of prandial premixed therapy using insulin lispro mix 50/50 3 times daily compared with progressive titration of insulin lispro mix 75/25 or biphasic insulin aspart 70/30 twice daily in patients with type 2 diabetes mellitus: a randomized, 16-week, open-label study. Clin Ther. 2011 Nov;33(11):1682-93. PMID: 22036246.
52. Feinglos M, Dailey G, Cefalu W, et al. Effect on glycemic control of the addition of 2.5 mg glipizide GITS to metformin in patients with T2DM. Diabetes Res Clin Pract. 2005 2005 May;68(2):167-75.
53. Ferrannini E, Berk A, Hantel S, et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: An active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care. 2013;36(12):4015-21.
54. Fidan E, Onder Ersoz H, Yilmaz M, et al. The effects of rosiglitazone and metformin on inflammation and endothelial dysfunction in patients with type 2 diabetes mellitus. Acta Diabetol. 2011 Dec;48(4):297-302. PMID: 21424914.
55. Fonseca V, Rosenstock J, Patwardhan R, et al. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. JAMA. 2000 2000 Apr 5;283(13):1695-702.
56. Fonseca V, Zhu T, Karyekar C, et al. Adding saxagliptin to extended-release metformin vs. uptitrating metformin dosage. Diabetes Obes Metab. 2012 Apr;14(4):365-71. PMID: 22192246.
57. Forst T, Uhlig-Laske B, Ring A, et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes. Diabet Med. 2010 Dec;27(12):1409-19. PMID: 21059094.
58. Forst T, Michelson G, Ratter F, et al. Addition of liraglutide in patients with Type 2 diabetes well controlled on metformin monotherapy improves several markers of vascular function. Diabet Med. 2012 Sep;29(9):1115-8. PMID: 22288732.
59. Forst T, Anastassiadis E, Diessel S, et al. Effect of linagliptin compared to glimepiride on postprandial glucose metabolism, islet cell function, and vascular function parameters in patients with type 2 diabetes mellitus on ongoing metformin treatment. Diabetes Metab Res Rev. 2014 Jan 23PMID: 24459063.
60. Gallwitz B, Bohmer M, Segiet T, et al. Exenatide twice daily versus premixed insulin aspart 70/30 in metformin-treated patients with type 2 diabetes: a randomized 26-week study on glycemic control and hypoglycemia. Diabetes Care. 2011 Mar;34(3):604-6. PMID: 21285388.
61. Gallwitz B, Rosenstock J, Rauch T, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet. 2012 Aug 4;380(9840):475-83. PMID: 22748821.
62. Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. Lancet. 2012 Jun 16;379(9833):2270-8. PMID: 22683137.
63. Garber AJ, Larsen J, Schneider SH, et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. Diabetes Obes Metab. 2002 2002 May;4(3):201-8.
64. Garber AJ, Donovan DSJ, Dandona P, et al. Efficacy of glyburide/metformin tablets compared with initial monotherapy in type 2 diabetes. J Clin Endocrinol Metab. 2003 2003 Aug;88(8):3598-604.
65. Garber A, Klein E, Bruce S, et al. Metformin-glibenclamide versus metformin plus rosiglitazone in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Diabetes Obes Metab. 2006 2006 Mar;8(2):156-63.
66. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009 2009 Feb 7;373(9662):473-81.
67. Garber A, Henry RR, Ratner R, et al. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. Diabetes Obes Metab. 2011 Apr;13(4):348-56. PMID: 21205128.
68. Genovese S, Passaro A, Brunetti P, et al. Pioglitazone Randomised Italian Study on Metabolic Syndrome (PRISMA): effect of pioglitazone with metformin on HDL-C levels in Type 2 diabetic patients. J Endocrinol Invest. 2013 Sep;36(8):606-16. PMID: 23511244.
69. Genovese S, De Berardis G, Nicolucci A, et al. Effect of pioglitazone versus metformin on cardiovascular risk markers in type 2 diabetes. Adv Ther. 2013 Feb;30(2):190-202. PMID: 23359066.
70. Goke B, Gallwitz B, Eriksson J, et al. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. Int J Clin Pract. 2010 Nov;64(12):1619-31. PMID: 20846286.
71. Goldstein BJ, Pans M, Rubin CJ. Multicenter, randomized, double-masked, parallel-group assessment of simultaneous glipizide/metformin as second-line pharmacologic treatment for patients with type 2 diabetes mellitus that is inadequately controlled by a sulfonylurea. Clin Ther. 2003 2003 Mar;25(3):890-903.
72. Goldstein BJ, Feinglos MN, Lunceford JK, et al. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care. 2007 2007 Aug;30(8):1979-87.
73. Gomez-Perez FJ, Fanghanel-Salmon G, Antonio Barbosa J, et al. Efficacy and safety of rosiglitazone plus metformin in Mexicans with type 2 diabetes. Diabetes Metab Res Rev. 2002 2002 Mar-Apr;18(2):127-34.

74. Gupta AK, Smith SR, Greenway FL, et al. Pioglitazone treatment in type 2 diabetes mellitus when combined with portion control diet modifies the metabolic syndrome. Diabetes Obes Metab. 2009 2009 Apr;11(4):330-7.
75. Gupta RK, Rehan HS, Rohatagi A, et al. The effect of glipizide, metformin and rosiglitazone on nontraditional cardiovascular risk factors in newly diagnosed patients with type 2 diabetes mellitus. International journal of diabetes in developing countries; 2010. p. 123-.
76. Gupta A, Ahmad Ansari N, Yadav N. Comparative efficacy and safety of sitagliptin and Glimepiride in patients of newly diagnosed type 2 diabetes mellitus. International Journal of Pharmaceutical Sciences Review and Research. 2013;23(2):137-41.
77. Haak T, Meinicke T, Jones R, et al. Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2012 Jun;14(6):565-74. PMID: 22356132.
78. Haak T, Meinicke T, Jones R, et al. Initial combination of linagliptin and metformin in patients with type 2 diabetes: efficacy and safety in a randomised, double-blind 1-year extension study. Int J Clin Pract. 2013 Dec;67(12):1283-93. PMID: 24118640.
79. Hallsten K, Virtanen KA, Lonnqvist F, et al. Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes. Diabetes. 2002 2002 Dec;51(12):3479-85.
80. Hamann A, Garcia-Puig J, Paul G, et al. Comparison of fixed-dose rosiglitazone/metformin combination therapy with sulphonylurea plus metformin in overweight individuals with Type 2 diabetes inadequately controlled on metformin alone. Exp Clin Endocrinol Diabetes. 2008 2008 Jan;116(1):6-13.
81. Hanefeld M, Brunetti P, Schernthaner GH, et al. One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. Diabetes Care. 2004 2004 Jan;27(1):141-7.
82. Hanefeld M, Patwardhan R, Jones NP. A one-year study comparing the efficacy and safety of rosiglitazone and glibenclamide in the treatment of type 2 diabetes. Nutr Metab Cardiovasc Dis. 2007 2007 Jan;17(1):13-23.
83. Haring HU, Merker L, Seewaldt-Becker E, et al. Empaglif lozin as add-on to metformin in patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014;37(6):1650-9.
84. Henry RR, Murray AV, Marmolejo MH, et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract. 2012 May;66(5):446-56. PMID: 22413962.
85. Hermann LS, Bitzen PO, Kjellstrom T, et al. Comparative efficacy of metformin and glibenclamide in patients with non-insulin-dependent diabetes mellitus. Diabete Metab. 1991 1991 May;17(1 Pt 2):201-8.
86. Hermann LS, Schersten B, Bitzen PO, et al. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care. 1994 1994 Oct;17(10):1100-9.
87. Hermans MP, Delibasi T, Farmer I, et al. Effects of saxagliptin added to sub-maximal doses of metformin compared with uptitration of metformin in type 2 diabetes: the PROMPT study. Curr Med Res Opin. 2012 Oct;28(10):1635-45. PMID: 23020253.
88. Home PD, Jones NP, Pocock SJ, et al. Rosiglitazone RECORD study: glucose control outcomes at 18 months. Diabet Med. 2007 2007 Jun;24(6):626-34.
89. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 2009 Jun 5.
90. Iliadis F, Kadoglou NP, Hatzitolios A, et al. Metabolic effects of rosiglitazone and metformin in Greek patients with recently diagnosed type 2 diabetes. In Vivo. 2007 2007 Nov-Dec;21(6):1107-14.
91. Jadzinsky M, Pfutzner A, Paz-Pacheco E, et al. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes Obes Metab. 2009 2009 Jun;11(6):611-22.
92. Jain R, Osei K, Kupfer S, et al. Long-term safety of pioglitazone versus glyburide in patients with recently diagnosed type 2 diabetes mellitus. Pharmacotherapy. 2006 2006 Oct;26(10):1388-95.
93. Ji L, Zinman B, Patel S, et al. Efficacy and safety of linagliptin co-administered with low-dose metformin once daily versus high-dose metformin twice daily in treatment-naive patients with type 2 diabetes: a double-blind randomized trial. Adv Ther. 2015 Mar;32(3):201-15. PMID: 25805187.
94. Jonker JT, Meer RWVD, Rijzewijk LJ, et al. A differential effect of pioglitazone versus metformin on fat depots in patients with type 2 diabetes mellitus. Diabetes. 2009;58((Jonker J.T.; Meer R.W.V.D.; Rijzewijk L.J.; Menting L.J.; Diamant M.; Roos A.D.; Lamb H.J.; Smit J.W.A.; Romijn J.A.)).
95. Kadoglou NP, Kapelouzou A, Tsanikidis H, et al. Effects of rosiglitazone/metformin fixed-dose combination therapy and metformin monotherapy on serum vaspin, adiponectin and IL-6 levels in drug-naive patients with type 2 diabetes. Exp Clin Endocrinol Diabetes. 2011 Feb;119(2):63-8. PMID: 21031343.
96. Kadowaki T, Tajima N, Odawara M, et al. Addition of sitagliptin to ongoing metformin monotherapy improves glycemic control in Japanese patients with type 2 diabetes over 52 weeks. J Diabetes Investig. 2013 Mar 18;4(2):174-81. PMID: 24843649.
97. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006 2006 Dec 7;355(23):2427-43.
98. Kaku K. Efficacy and safety of therapy with metformin plus pioglitazone in the treatment of patients with type 2 diabetes: a double-blind, placebo-controlled, clinical trial. Curr Med Res Opin. 2009 2009 May;25(5):1111-9.

99. Kaku K, Rasmussen MF, Nishida T, et al. Fifty-two-week, randomized, multicenter trial to compare the safety and efficacy of the novel glucagon-like peptide-1 analog liraglutide vs glibenclamide in patients with type 2 diabetes. J Diabetes Investig. 2011 Nov 30;2(6):441-7. PMID: 24843528.
100. Kato T, Sawai Y, Kanayama H, et al. Comparative study of low-dose pioglitazone or metformin treatment in Japanese diabetic patients with metabolic syndrome. Exp Clin Endocrinol Diabetes. 2009 Nov;117(10):593-9. PMID: 19924605.
101. Kikuchi M, Kaku K, Odawara M, et al. Efficacy and tolerability of rosiglitazone and pioglitazone in drug-naive Japanese patients with type 2 diabetes mellitus: a double-blind, 28 weeks' treatment, comparative study. Curr Med Res Opin. 2012 Jun;28(6):1007-16. PMID: 22587483.
102. Kim HJ, Kang ES, Kim DJ, et al. Effects of rosiglitazone and metformin on inflammatory markers and adipokines: decrease in interleukin-18 is an independent factor for the improvement of homeostasis model assessment-beta in type 2 diabetes mellitus. Clin Endocrinol (Oxf). 2007 2007 Feb;66(2):282-9.
103. Kim HS, Kim DM, Cha BS, et al. Efficacy of glimepiride/metformin fixed-dose combination vs metformin uptitration in type 2 diabetic patients inadequately controlled on low-dose metformin monotherapy: A randomized, open label, parallel group, multicenter study in Korea. Journal of Diabetes Investigation. 2014((Kim H.-S.) Department of Internal Medicine Keimyung University School of Medicine Daegu Korea).
104. Kiyici S, Ersoy C, Kaderli A, et al. Effect of rosiglitazone, metformin and medical nutrition treatment on arterial stiffness, serum MMP-9 and MCP-1 levels in drug naive type 2 diabetic patients. Diabetes Research and Clinical Practice. 2009 2009/10//;86(1):44-50.
105. Kvapil M, Swatko A, Hilberg C, et al. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. Diabetes Obes Metab. 2006 2006 Jan;8(1):39-48.
106. Lavalle-Gonzalez FJ, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia. 2013 Dec;56(12):2582-92. PMID: 24026211.
107. Lawrence JM, Reid J, Taylor GJ, et al. Favorable effects of pioglitazone and metformin compared with gliclazide on lipoprotein subfractions in overweight patients with early type 2 diabetes. Diabetes Care. 2004 2004 Jan;27(1):41-6.
108. Leiter LA, Harris SB, Chiasson J-L, et al. Efficacy and safety of Rosiglitazone as monotherapy or in combination with metformin in primary care settings. Can. J. Diabetes. 2005 2005;29(4):384-92.
109. List JF, Woo V, Morales E, et al. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care. 2009 Apr;32(4):650-7. PMID: 19114612.
110. Madsbad S, Schmitz O, Ranstam J, et al. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. Diabetes Care. 2004 2004 Jun;27(6):1335-42.
111. Maffioli P, Fogari E, D'Angelo A, et al. Ultrasonography modifications of visceral and subcutaneous adipose tissue after pioglitazone or glibenclamide therapy combined with rosuvastatin in type 2 diabetic patients not well controlled by metformin. Eur J Gastroenterol Hepatol. 2013 Sep;25(9):1113-22. PMID: 23524525.
112. Malone JK, Beattie SD, Campaigne BN, et al. Therapy after single oral agent failure: adding a second oral agent or an insulin mixture? Diabetes Res Clin Pract. 2003 2003 Dec;62(3):187-95.
113. Marre M, Howlett H, Lehert P, et al. Improved glycaemic control with metformin-glibenclamide combined tablet therapy (Glucovance) in Type 2 diabetic patients inadequately controlled on metformin. Diabet Med. 2002 2002 Aug;19(8):673-80.
114. Moon JS, Ha KS, Yoon JS, et al. The effect of glargine versus glimepiride on pancreatic beta-cell function in patients with type 2 diabetes uncontrolled on metformin monotherapy: open-label, randomized, controlled study. Acta Diabetol. 2014 Apr;51(2):277-85. PMID: 24445656.
115. Nakamura T, Ushiyama C, Shimada N, et al. Comparative effects of pioglitazone, glibenclamide, and voglibose on urinary endothelin-1 and albumin excretion in diabetes patients. J Diabetes Complications. 2000 2000 Sep-Oct;14(5):250-4.
116. Nakamura T, Matsuda T, Kawagoe Y, et al. Effect of pioglitazone on carotid intima-media thickness and arterial stiffness in type 2 diabetic nephropathy patients. Metabolism. 2004 2004 Oct;53(10):1382-6.
117. Natali A, Baldeweg S, Toschi E, et al. Vascular effects of improving metabolic control with metformin or rosiglitazone in type 2 diabetes. Diabetes Care. 2004 2004 Jun;27(6):1349-57.
118. Nauck MA, Meininger G, Sheng D, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007 2007 Mar;9(2):194-205.
119. Nauck MA, Ellis GC, Fleck PR, et al. Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. Int J Clin Pract. 2009 Jan;63(1):46-55. PMID: 19125992.
120. Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care. 2011 Sep;34(9):2015-22. PMID: 21816980.
121. Nauck M, Weinstock RS, Umpierrez GE, et al. Efficacy and Safety of Dulaglutide Versus Sitagliptin After 52 Weeks in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-5). Diabetes Care. 2014 Apr 17PMID: 24742660.
122. Oz Gul O, Tuncel E, Yilmaz Y, et al. Comparative effects of pioglitazone and rosiglitazone on plasma levels of soluble receptor for advanced glycation end products in type 2 diabetes mellitus patients. Metabolism. 2010 Jan;59(1):64-9. PMID: 19709689.

123. Pavo I, Jermendy G, Varkonyi TT, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. J Clin Endocrinol Metab. 2003 2003 Apr;88(4):1637-45.
124. Perez-Monteverde A, Seck T, Xu L, et al. Efficacy and safety of sitagliptin and the fixed-dose combination of sitagliptin and metformin vs. pioglitazone in drug-naive patients with type 2 diabetes. Int J Clin Pract. 2011 Sep;65(9):930-8. PMID: 21849007.
125. Perez A, Zhao Z, Jacks R, et al. Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM. Curr Med Res Opin. 2009 Dec;25(12):2915-23. PMID: 19827910.
126. Petrica L, Petrica M, Vlad A, et al. Nephro- and neuroprotective effects of rosiglitazone versus glimepiride in normoalbuminuric patients with type 2 diabetes mellitus: a randomized controlled trial. Wien Klin Wochenschr. 2009;121(23-24):765-75. PMID: 20047115.
127. Pfutzner A, Marx N, Lubben G, et al. Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. J Am Coll Cardiol. 2005 2005 Jun 21;45(12):1925-31.
128. Pfutzner A, Schondorf T, Tschope D, et al. PIOfix-study: effects of pioglitazone/metformin fixed combination in comparison with a combination of metformin with glimepiride on diabetic dyslipidemia. Diabetes Technol Ther. 2011 Jun;13(6):637-43. PMID: 21457065.
129. Pfutzner A, Paz-Pacheco E, Allen E, et al. Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks. Diabetes Obes Metab. 2011 Jun;13(6):567-76. PMID: 21342412.
130. Pratley RE, Nauck M, Bailey T, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet. 2010 Apr 24;375(9724):1447-56. PMID: 20417856.
131. Pratley RE, Fleck P, Wilson C. Efficacy and safety of initial combination therapy with alogliptin plus metformin versus either as monotherapy in drug-naive patients with type 2 diabetes: a randomized, double-blind, 6-month study. Diabetes Obes Metab. 2014 Jul;16(7):613-21. PMID: 24400655.
132. Qiu R, Capuano G, Meininger G. Efficacy and safety of twice-daily treatment with canagliflozin, a sodium glucose co-transporter 2 inhibitor, added on to metformin monotherapy in patients with type 2 diabetes mellitus. Journal of Clinical and Translational Endocrinology. 2014;1(2):54-60.
133. Ramachandran A, Snehalatha C, Salini J, et al. Use of glimepiride and insulin sensitizers in the treatment of type 2 diabetes--a study in Indians. J Assoc Physicians India. 2004 2004 Jun;52:459-63.
134. Raskin PR, Hollander PA, Lewin A, et al. Basal insulin or premix analogue therapy in type 2 diabetes patients. Eur J Intern Med. 2007 2007 Jan;18(1):56-62.
135. Reasner C, Olansky L, Seck TL, et al. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2011 Jul;13(7):644-52. PMID: 21410627.
136. Ridderstrale M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. The Lancet Diabetes and Endocrinology. 2014((Ridderstrale M., mtrd@steno.dk) Steno Diabetes Center, Gentofte, Denmark).
137. Rigby SP, Handelsman Y, Lai YL, et al. Effects of colesevelam, rosiglitazone, or sitagliptin on glycemic control and lipid profile in patients with type 2 diabetes mellitus inadequately controlled by metformin monotherapy. Endocr Pract. 2010 Jan-Feb;16(1):53-63. PMID: 19789153.
138. Robbins DC, Beisswenger PJ, Ceriello A, et al. Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. Clin Ther. 2007 2007 Nov;29(11):2349-64.
139. Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Diabetes and Endocrinology; 2013. p. 208-19.
140. Rosenstock J, Rood J, Cobitz A, et al. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab. 2006 2006 Nov;8(6):650-60.
141. Rosenstock J, Inzucchi SE, Seufert J, et al. Initial combination therapy with alogliptin and pioglitazone in drug-naive patients with type 2 diabetes. Diabetes Care. 2010 Nov;33(11):2406-8. PMID: 20724648.
142. Rosenstock J, Aggarwal N, Polidori D, et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care. 2012 Jun;35(6):1232-8. PMID: 22492586.
143. Rosenstock J, Wilson C, Fleck P. Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study. Diabetes Obes Metab. 2013 Oct;15(10):906-14. PMID: 23531118.
144. Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab; 2013. p. 1154-60.

145. Rosenstock J, Hansen L, Zee P, et al. Dual Add-on Therapy in Type 2 Diabetes Poorly Controlled With Metformin Monotherapy: A Randomized Double-Blind Trial of Saxagliptin Plus Dapagliflozin Addition Versus Single Addition of Saxagliptin or Dapagliflozin to Metformin. Diabetes Care. 2015 Mar;38(3):376-83. PMID: 25352655.
146. Ross SA, Rafeiro E, Meinicke T, et al. Efficacy and safety of linagliptin 2.5?mg twice daily versus 5?mg once daily in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, placebo-controlled trial. Curr Med Res Opin; 2012. p. 1465-74.
147. Russell-Jones D, Cuddihy RM, Hanefeld M, et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. Diabetes Care. 2012 Feb;35(2):252-8. PMID: 22210563.
148. Schernthaner G, Duran-Garcia S, Hanefeld M, et al. Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). Diabetes Obes Metab. 2015 Jul;17(7):630-8. PMID: 25761977.
149. Schernthaner G, Matthews DR, Charbonnel B, et al. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. J Clin Endocrinol Metab. 2004 2004 Dec;89(12):6068-76.
150. Schondorf T, Musholt PB, Hohberg C, et al. The fixed combination of pioglitazone and metformin improves biomarkers of platelet function and chronic inflammation in type 2 diabetes patients: results from the PIOfix study. J Diabetes Sci Technol. 2011 Mar;5(2):426-32. PMID: 21527115.
151. Schumm-Draeger PM, Burgess L, Koranyi L, et al. Twice-daily dapagliflozin co-administered with metformin in type 2 diabetes: a 16-week randomized, placebo-controlled clinical trial. Diabetes Obes Metab. 2015 Jan;17(1):42-51. PMID: 25200570.
152. Scott R, Wu M, Sanchez M, et al. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. Int J Clin Pract. 2007 2007 Jan;61(1):171-80.
153. Scott R, Loeys T, Davies MJ, et al. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. Diabetes Obes Metab. 2008 2008 Sep;10(10):959-69.
154. Seck T, Nauck M, Sheng D, et al. Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. Int J Clin Pract. 2010 Apr;64(5):562-76. PMID: 20456211.
155. Seino Y, Rasmussen MF, Nishida T, et al. Efficacy and safety of the once-daily human GLP-1 analogue, liraglutide, vs glibenclamide monotherapy in Japanese patients with type 2 diabetes. Curr Med Res Opin. 2010 May;26(5):1013-22. PMID: 20199137.
156. Seino Y, Miyata Y, Hiroi S, et al. Efficacy and safety of alogliptin added to metformin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label, long-term extension study. Diabetes Obes Metab. 2012 Oct;14(10):927-36. PMID: 22583697.
157. Shihara N, Kitaoka M, Inagaki N, et al. Randomized controlled trial of single-agent glimepiride and pioglitazone in Japanese patients with type 2 diabetes: A comparative study. J Diabetes Investig. 2011 Oct 7;2(5):391-8. PMID: 24843519.
158. Srivastava S, Saxena GN, Keshwani P, et al. Comparing the efficacy and safety profile of sitagliptin versus glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone. J Assoc Physicians India. 2012 Mar;60:27-30. PMID: 22799111.
159. St John Sutton M, Rendell M, Dandona P, et al. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. Diabetes Care. 2002 2002 Nov;25(11):2058-64.
160. Stewart MW, Cirkel DT, Furuseth K, et al. Effect of metformin plus roziglitazone compared with metformin alone on glycaemic control in well-controlled Type 2 diabetes. Diabet Med. 2006 2006 Oct;23(10):1069-78.
161. Suzuki K, Tanaka S, Aoki C, et al. Greater efficacy and improved endothelial dysfunction in untreated type 2 diabetes with liraglutide versus sitagliptin. Dokkyo Journal of Medical Sciences. 2014;41(3):211-20.
162. Tan MH, Johns D, Strand J, et al. Sustained effects of pioglitazone vs. glibenclamide on insulin sensitivity, glycaemic control, and lipid profiles in patients with Type 2 diabetes. Diabet Med. 2004 2004 Aug;21(8):859-66.
163. Tan M, Johns D, Gonzalez Galvez G, et al. Effects of pioglitazone and glimepiride on glycemic control and insulin sensitivity in Mexican patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, parallel-group trial. Clin Ther. 2004 2004 May;26(5):680-93.
164. Taskinen MR, Rosenstock J, Tamminen I, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2011 Jan;13(1):65-74. PMID: 21114605.
165. Taslimi S, Esteghamati A, Rashidi A, et al. Treatment with pioglitazone is associated with decreased preprandial ghrelin levels: a randomized clinical trial. Peptides. 2013 Feb;40:89-92. PMID: 23276779.
166. Teramoto T, Yamada N, Shirai K, et al. Effects of pioglitazone hydrochloride on Japanese patients with type 2 diabetes mellitus. J Atheroscler Thromb. 2007 2007 Apr;14(2):86-93.
167. Tosi F, Muggeo M, Brun E, et al. Combination treatment with metformin and glibenclamide versus single-drug therapies in type 2 diabetes mellitus: a randomized, double-blind, comparative study. Metabolism. 2003 2003 Jul;52(7):862-7.
168. Turkmen Kemal Y, Guvener Demirag N, Yildirir A, et al. Effects of rosiglitazone on plasma brain natriuretic peptide levels and myocardial performance index in patients with type 2 diabetes mellitus. Acta Diabetol. 2007 2007 Sep;44(3):149-56.

169. Turner RC, Cull CA, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA. 1999 1999 Jun 2;281(21):2005-12.
170. Umpierrez G, Issa M, Vlajnic A. Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial. Curr Med Res Opin. 2006 2006 Apr;22(4):751-9.
171. Umpierrez G, Povedano ST, Manghi FP, et al. Efficacy and Safety of Dulaglutide Monotherapy Versus Metformin in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-3). Diabetes Care. 2014 May 19PMID: 24842985.
172. van der Meer RW, Rijzewijk LJ, de Jong HW, et al. Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled type 2 diabetes mellitus. Circulation. 2009 2009 Apr 21;119(15):2069-77.
173. Wang W, Yang J, Yang G, et al. Efficacy and safety of linagliptin in Asian patients with type 2 diabetes mellitus inadequately controlled by metformin: A multinational 24-week, randomized clinical trial. J Diabetes. 2015 Mar 6PMID: 25753488.
174. Weissman P, Goldstein BJ, Rosenstock J, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. Curr Med Res Opin. 2005 2005 Dec;21(12):2029-35.
175. White JL, Buchanan P, Li J, et al. A randomized controlled trial of the efficacy and safety of twice-daily saxagliptin plus metformin combination therapy in patients with type 2 diabetes and inadequate glycemic control on metformin monotherapy. BMC Endocr Disord. 2014;14(1):17. PMID: 24565221.
176. Williams-Herman D, Johnson J, Teng R, et al. Efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: a 54-week study. Curr Med Res Opin. 2009 2009 Mar;25(3):569-83.
177. Williams-Herman D, Johnson J, Teng R, et al. Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. Diabetes Obes Metab. 2010 May;12(5):442-51. PMID: 20415693.
178. Xu W, Bi Y, Sun Z, et al. Comparison of the effects on glycaemic control and beta-cell function in newly diagnosed type 2 diabetes patients of treatment with exenatide, insulin or pioglitazone: a multicentre randomized parallel-group trial (the CONFIDENCE study). J Intern Med. 2015 Jan;277(1):137-50. PMID: 25039675.
179. Yamanouchi T, Sakai T, Igarashi K, et al. Comparison of metabolic effects of pioglitazone, metformin, and glimepiride over 1 year in Japanese patients with newly diagnosed Type 2 diabetes. Diabet Med. 2005 2005 Aug;22(8):980-5.
180. Yang W, Pan CY, Tou C, et al. Efficacy and safety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Res Clin Pract. 2011 Nov;94(2):217-24. PMID: 21871686.
181. Yang W, Chen L, Ji Q, et al. Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial(*). Diabetes Obes Metab. 2011 Jan;13(1):81-8. PMID: 21114607.
182. Yang W, Guan Y, Shentu Y, et al. The addition of sitagliptin to ongoing metformin therapy significantly improves glycemic control in Chinese patients with type 2 diabetes. J Diabetes. 2012 Sep;4(3):227-37. PMID: 22672586.
183. Yoon KH, Shin JA, Kwon HS, et al. Comparison of the efficacy of glimepiride, metformin, and rosiglitazone monotherapy in korean drug-naive type 2 diabetic patients: the practical evidence of antidiabetic monotherapy study. Diabetes Metab J. 2011 Feb;35(1):26-33. PMID: 21537410.
184. Yuan GH, Song WL, Huang YY, et al. Efficacy and tolerability of exenatide monotherapy in obese patients with newly diagnosed type 2 diabetes: a randomized, 26 weeks metformin-controlled, parallel-group study. Chin Med J (Engl). 2012 Aug;125(15):2677-81. PMID: 22931974.
185. Nakamura T, Sugaya T, Kawagoe Y, et al. Effect of pioglitazone on urinary liver-type fatty acid-binding protein concentrations in diabetes patients with microalbuminuria. Diabetes Metab Res Rev. 2006 2006 Sep-Oct;22(5):385-9.
186. Amador-Licona N, Guizar-Mendoza J, Vargas E, et al. The short-term effect of a switch from glibenclamide to metformin on blood pressure and microalbuminuria in patients with type 2 diabetes mellitus. Arch Med Res. 2000 2000 Nov-Dec;31(6):571-5.
187. Zhang H, Zhang X, Hu C, et al. Exenatide reduces urinary transforming growth factor-beta1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria. Kidney Blood Press Res. 2012;35(6):483-8. PMID: 22687869.
188. Raz I, Chen Y, Wu M, et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. Curr Med Res Opin. 2008 2008 Feb;24(2):537-50.
189. Agarwal R, Saha C, Battiwala M, et al. A pilot randomized controlled trial of renal protection with pioglitazone in diabetic nephropathy. Kidney Int. 2005 2005 Jul;68(1):285-92.
190. Andersson C, Olesen JB, Hansen PR, et al. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. Diabetologia. 2010 Dec;53(12):2546-53. PMID: 20838985.
191. Brownstein JS, Murphy SN, Goldfine AB, et al. Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records. Diabetes Care. 2010 2010 Mar;33(3):526-31.
192. Corrao G, Romio SA, Zambon A, et al. Multiple outcomes associated with the use of metformin and sulphonylureas in type 2 diabetes: a population-based cohort study in Italy. Eur J Clin Pharmacol. 2011 Mar;67(3):289-99. PMID: 21088829.

193. Ekstrom N, Schioler L, Svensson AM, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open. 2012;2(4)PMID: 22798258.
194. Ferrannini E, Seman L, Seewaldt-Becker E, et al. A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2013;15(8):721-8.
195. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013 May;36(5):1304-11. PMID: 23230096.
196. Horsdal HT, Sondergaard F, Johnsen SP, et al. Antidiabetic treatments and risk of hospitalisation with myocardial infarction: a nationwide case-control study. Pharmacoepidemiol Drug Saf. 2011 Apr;20(4):331-7. PMID: 21442682.
197. Hsiao FY. Does cardiovascular risk decrease after discontinuing rosiglitazone use? Early and late effects of rosiglitazone on the risk of myocardial infarction in type 2 diabetic patients. Drug Information Journal. 2009;43(4):521.
198. Hung AM, Roumie CL, Greevy RA, et al. Comparative effectiveness of incident oral antidiabetic drugs on kidney function. Kidney Int. 2012 Apr;81(7):698-706. PMID: 22258320.
199. Hung YC, Lin CC, Wang TY, et al. Oral hypoglycaemic agents and the development of non-fatal cardiovascular events in patients with type 2 diabetes mellitus. Diabetes Metab Res Rev. 2013 Nov;29(8):673-9. PMID: 23956007.
200. Hung AM, Roumie CL, Greevy RA, et al. Kidney function decline in metformin versus sulfonylurea initiators: assessment of time-dependent contribution of weight, blood pressure, and glycemic control. Pharmacoepidemiol Drug Saf. 2013 Jun;22(6):623-31. PMID: 23592561.
201. Johnson JA, Simpson SH, Toth EL, et al. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 diabetes. Diabet Med. 2005 2005 Apr;22(4):497-502.
202. Jones TA, Sautter M, Van Gaal LF, et al. Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes. Diabetes Obes Metab. 2003 2003 May;5(3):163-70.
203. Kahler KH, Rajan M, Rhoads GG, et al. Impact of oral antihyperglycemic therapy on all-cause mortality among patients with diabetes in the Veterans Health Administration. Diabetes Care. 2007 2007 Jul;30(7):1689-93.
204. Malone JK, Kerr LF, Campaigne BN, et al. Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clin Ther. 2004 2004 Dec;26(12):2034-44.
205. Malone JK, Bai S, Campaigne BN, et al. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. Diabet Med. 2005 2005 Apr;22(4):374-81.
206. Masica AL, Ewen E, Daoud YA, et al. Comparative effectiveness research using electronic health records: impacts of oral antidiabetic drugs on the development of chronic kidney disease. Pharmacoepidemiol Drug Saf. 2013 Apr;22(4):413-22. PMID: 23436488.
207. Mogensen UM, Andersson C, Fosbol EL, et al. Cardiovascular safety of combination therapies with incretin-based drugs and metformin compared with a combination of metformin and sulphonylurea in type 2 diabetes mellitus - a retrospective nationwide study. Diabetes Obes Metab. 2014 May 14PMID: 24827939.
208. Pantalone KM, Kattan MW, Yu C, et al. The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. Acta Diabetol. 2009 2009 Jun;46(2):145-54.
209. Pantalone KM, Kattan MW, Yu C, et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. Diabetes Obes Metab. 2012 Sep;14(9):803-9. PMID: 22486923.
210. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med. 2012 Nov 6;157(9):601-10. PMID: 23128859.
211. Scheller NM, Mogensen UM, Andersson C, et al. All-cause mortality and cardiovascular effects associated with the DPP-IV inhibitor sitagliptin compared with metformin, a retrospective cohort study on the Danish population. Diabetes, Obesity and Metabolism. 2014;16(3):231-6.
212. Schramm TK, Gislason GH, Vaag A, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J. 2011 Aug;32(15):1900-8. PMID: 21471135.
213. Stenlof K, Cefalu WT, Kim KA, et al. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Curr Med Res Opin. 2014 Feb;30(2):163-75. PMID: 24073995.
214. Wheeler S, Moore K, Forsberg CW, et al. Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea or rosiglitazone monotherapy. Diabetologia. 2013 Jun 25PMID: 23797633.
215. Hsiao FY, Huang WF, Wen YW, et al. Thiazolidinediones and cardiovascular events in patients with type 2 diabetes mellitus: a retrospective cohort study of over 473,000 patients using the National Health Insurance database in Taiwan. Drug Saf. 2009 2009;32(8):675-90.
216. Curkendall SM, Zhang B, Lenhart G, et al. Rate of hypoglycemia in patients with type 2 diabetes receiving metformin plus saxagliptin versus metformin plus sulfonylurea: A retrospective observational cohort study using administrative claims data. Expert Review of Endocrinology and Metabolism. 2014;9(2):183-91.

217. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia. 2009 2009 Sep;52(9):1766-77.
218. Davies M, Heller S, Sreenan S, et al. Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. Diabetes Care. 2013 May;36(5):1368-76. PMID: 23275363.
219. Dormuth CR, Carney G, Carleton B, et al. Thiazolidinediones and fractures in men and women. Arch Intern Med. 2009 2009 Aug 10;169(15):1395-402.
220. Kahn SE, Zinman B, Lachin JM, et al. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care. 2008 2008 May;31(5):845-51.
221. Karter AJ, Ahmed AT, Liu J, et al. Pioglitazone initiation and subsequent hospitalization for congestive heart failure. Diabet Med. 2005 2005 Aug;22(8):986-93.
222. Komajda M, McMurray JJ, Beck-Nielsen H, et al. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. Eur Heart J. 2010 Apr;31(7):824-31. PMID: 20118174.
223. Lee YK, Song SO, Kim KJ, et al. Glycemic Effectiveness of Metformin-Based Dual-Combination Therapies with Sulphonylurea, Pioglitazone, or DPP4-Inhibitor in Drug-Naive Korean Type 2 Diabetic Patients. Diabetes Metab J. 2013 Dec;37(6):465-74. PMID: 24404518.
224. Lehman DM, Lorenzo C, Hernandez J, et al. Statin use as a moderator of metformin effect on risk for prostate cancer among type 2 diabetic patients. Diabetes Care. 2012 May;35(5):1002-7. PMID: 22456867.
225. Rajagopalan R, Iyer S, Perez A. Comparison of pioglitazone with other antidiabetic drugs for associated incidence of liver failure: no evidence of increased risk of liver failure with pioglitazone. Diabetes Obes Metab. 2005 2005 Mar;7(2):161-9.
226. Skrivanek Z, Gaydos BL, Chien JY, et al. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). Diabetes Obes Metab. 2014 Apr 25PMID: 24762094.
227. Weir MA, Gomes T, Mamdani M, et al. Impaired renal function modifies the risk of severe hypoglycaemia among users of insulin but not glyburide: a population-based nested case-control study. Nephrol Dial Transplant. 2011 Jun;26(6):1888-94. PMID: 20974644.
228. Wright AD, Cull CA, Macleod KM, et al. Hypoglycemia in Type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications. 2006 2006 Nov-Dec;20(6):395-401.
229. Bunck MC, Diamant M, Corner A, et al. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes Care. 2009 2009 May;32(5):762-8.
230. van Staa TP, Patel D, Gallagher AM, et al. Glucose-lowering agents and the patterns of risk for cancer: a study with the General Practice Research Database and secondary care data. Diabetologia. 2012 Mar;55(3):654-65. PMID: 22127412.
231. Kawai T, Funae O, Shimada A, et al. Effects of pretreatment with low-dose metformin on metabolic parameters and weight gain by pioglitazone in Japanese patients with type 2 diabetes. Intern Med. 2008 2008;47(13):1181-8.
232. Gallwitz B, Rosenstock J, Patel S, et al. Regardless of the degree of glycaemic control, linagliptin has lower hypoglycaemia risk than all doses of glimepiride, at all time points, over the course of a 2-year trial. Diabetes Obes Metab. 2015 Mar;17(3):276-84. PMID: 25425502.
233. . United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. United Kingdom Prospective Diabetes Study Group. Ann Intern Med. 1998 1998 Feb 1;128(3):165-75.
234. Leiter LA, Carr MC, Stewart M, et al. Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study. Diabetes Care. 2014 Oct;37(10):2723-30. PMID: 25048383.
235. Merker L, Haering HU, Christiansen AV. LBSU-1082: Empagliflozin (EMPA) for >= 76 weeks as add-on to metformin un patients with type 2 diabetes (T2DM). 2014.
236. Belcher G, Lambert C, Goh KL, et al. Cardiovascular effects of treatment of type 2 diabetes with pioglitazone, metformin and gliclazide. Int J Clin Pract. 2004 2004 Sep;58(9):833-7.
237. Lester JW, Fernandes AW. Pioglitazone in a subgroup of patients with type 2 diabetes meeting the criteria for metabolic syndrome. Int J Clin Pract. 2005 2005 Feb;59(2):134-42.
238. Belcher G, Schernthaner G. Changes in liver tests during 1-year treatment of patients with Type 2 diabetes with pioglitazone, metformin or gliclazide. Diabet Med. 2005 2005 Aug;22(8):973-9.
239. Belcher G, Lambert C, Edwards G, et al. Safety and tolerability of pioglitazone, metformin, and gliclazide in the treatment of type 2 diabetes. Diabetes Res Clin Pract. 2005 2005 Oct;70(1):53-62.
240. Charbonnel B, Schernthaner G, Brunetti P, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. Diabetologia. 2005 2005 Jun;48(6):1093-104.
241. Ceriello A, Johns D, Widel M, et al. Comparison of effect of pioglitazone with metformin or sulfonylurea (monotherapy and combination therapy) on postload glycemia and composite insulin sensitivity index during an oral glucose tolerance test in patients with type 2 diabetes. Diabetes Care. 2005 2005 Feb;28(2):266-72.

242. Rendell MS, Glazer NB, Ye Z. Combination therapy with pioglitazone plus metformin or sulfonylurea in patients with Type 2 diabetes: influence of prior antidiabetic drug regimen. J Diabetes Complications. 2003 2003 Jul-Aug;17(4):211-7.
243. Del Prato S, Taskinen MR, Owens DR, et al. Efficacy and safety of linagliptin in subjects with type 2 diabetes mellitus and poor glycemic control: pooled analysis of data from three placebo-controlled phase III trials. J Diabetes Complications. 2013 May-Jun;27(3):274-9. PMID: 23403068.
244. Sjostrand M, Iqbal N, Lu J, et al. Saxagliptin improves glycemic control by modulating postprandial glucagon and C-peptide levels in Chinese patients with type 2 diabetes. Diabetes Res Clin Pract. 2014 May 29PMID: 24947443.
245. Davidson JA. Tolerability of saxagliptin in patients with inadequately controlled type 2 diabetes: results from 6 phase III studies. J Manag Care Pharm. 2014 Feb;20(2):120-9. PMID: 24456313.
246. Grimm M, Li Y, Brunell SC, et al. Exenatide once weekly versus daily basal insulin as add-on treatment to metformin with or without a sulfonylurea: a retrospective pooled analysis in patients with poor glycemic control. Postgrad Med. 2013 Sep;125(5):101-8. PMID: 24113668.
247. Rosenstock J, Gross JL, Aguilar-Salinas C, et al. Long-term 4-year safety of saxagliptin in drug-naive and metformin-treated patients with Type 2 diabetes. Diabet Med. 2013 Dec;30(12):1472-6. PMID: 23802840.
248. Karyekar C, Donovan M, Allen E, et al. Efficacy and safety of saxagliptin combination therapy in US patients with type 2 diabetes. Postgrad Med. 2011 Jul;123(4):63-70. PMID: 21680990.
249. Home PD, Kahn SE, Jones NP, et al. Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials. Diabetologia. 2010 Sep;53(9):1838-45. PMID: 20532476.
250. Jendle J, Nauck MA, Matthews DR, et al. Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. Diabetes Obes Metab. 2009 Dec;11(12):1163-72. PMID: 19930006.
251. Bailey RA, Vijapurkar U, Meininger G, et al. Diabetes-Related Composite Quality End Point Attainment: Canagliflozin Versus Sitagliptin Based on a Pooled Analysis of 2 Clinical Trials. Clin Ther. 2015 May 1;37(5):1045-54. PMID: 25795432.