Effective Health Care Program

Comparative Effectiveness Review
Number 34

Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension: An Update

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

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 are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

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 e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension: An Update

Structured Abstract

Objectives. A 2007 comparative effectiveness review (CER) evaluated the long-term benefits and harms of angiotensin-converting enzyme inhibitors (ACEIs) versus angiotensin II receptor blockers/antagonists (ARBs) for treating essential hypertension in adults. Since then, significant additional research has been published comparing these agents, and direct renin inhibitors (DRIs) have been introduced to the market. We sought to update 2007 CER on ACEIs versus ARBs and expand this to include comparisons with DRIs.

Data Sources. We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, a list of systematic reviews underway in the Cochrane Hypertension Review Group, and selected gray literature sources.

Review Methods. We included studies that directly compared ACEIs, ARBs, and/or DRIs in at least 20 total adults with essential hypertension; had at least 12 weeks of followup; and reported at least one outcome of interest. Two investigators reviewed each article, and a standard protocol was used to extract data on study design, interventions, population characteristics, and outcomes; evaluate study quality; and summarize the evidence. When appropriate, quantitative meta-analysis was performed.

Results. We included 97 studies (36 new since 2007) directly comparing ACEIs versus ARBs and 3 studies directly comparing DRIs to ACEIs or ARBs. The strength of evidence remains high for equivalence between ACEIs and ARBs for blood pressure lowering and use of a single antihypertensive agent, and for superiority of ARBs over ACEIs for short-term adverse events (primarily due to cough). The new evidence did not strengthen our conclusions regarding long-term cardiovascular outcomes, quality of life, progression of renal disease, medication adherence or persistence, rates of angioedema, or differences in key patient subgroups: the strength of evidence for these outcomes remained low to moderate. For DRIs, we were not able to reach definitive conclusions for any of the outcomes of interest. Few studies involved a representative sample treated in a typical clinical setting over a long duration; treatment protocols had marked heterogeneity; and significant amounts of data about important outcomes and patient subgroups were missing.

Conclusions. Evidence does not support a meaningful difference between ACEIs and ARBs for any outcome except short-term adverse events. Few, if any, of the questions that were not answered in the 2007 CER have been addressed by the 39 new studies. Future research in this area should consider areas of uncertainty and be prioritized accordingly.

Contents

Tables

Figures

Appendixes

Executive Summary

Background

Almost 75 million American adults—approximately one-third—have hypertension. The prevalence of hypertension increases with advancing age such that more than half of people 55 to 74 years old and approximately three-fourths of those age 75 years and older are affected. In addition to being the primary attributable risk factor for death throughout the world, hypertension results in substantial morbidity because of its impact on numerous target organs, including the brain, eyes, heart, arteries, and kidneys.

Despite the high rates of morbidity and mortality attributable to hypertension, control of the condition remains suboptimal. In addition to several effective nonpharmacological interventions—including diet, exercise, and control of body weight—many people require antihypertensive medication to lower blood pressure.

Among the many choices in antihypertensive therapy, some of the most common are those aimed at affecting the renin-angiotensin-aldosterone (renin) system. The renin system is an important mediator of blood volume, arterial pressure, and cardiac and vascular function. Components of this system can be identified in many tissues, but the primary site of renin release is the kidney. The renin system can be triggered by sympathetic stimulation, renal artery hypotension, and decreased sodium delivery to the distal tubule. Through proteolytic cleavage, renin acts on the oligopeptide substrate angiotensinogen to produce the decapeptide angiotensin I. In turn, two terminal peptide residues of angiotensin I are removed by the angiotensin-converting enzyme (ACE) to form the octapeptide angiotensin II. Angiotensin II acts directly on the resistance vessels to: increase systemic vascular resistance and arterial pressure; stimulate the adrenal cortex to release aldosterone, which leads to increased sodium and water reabsorption and potassium excretion; promote secretion of antidiuretic hormone, which leads to fluid retention; stimulate thirst; promote adrenergic function; and increase cardiac and vascular hypertrophy.

Therapies aimed at modifying the renin system have been used extensively for treatment of hypertension, heart failure, myocardial infarction, diabetes, and renal disease. Currently, three classes of drugs that interact with this system are used to inhibit the effects of angiotensin II: the angiotensin-converting enzyme inhibitors (ACEIs), the angiotensin II receptor blockers/antagonists (ARBs), and the direct renin inhibitors. ACEIs block the conversion of angiotensin I into angiotensin II; ARBs selectively inhibit angiotensin II from activating the angiotensin-specific receptor (AT1); and direct renin inhibitors block the conversion of angiotensinogen into angiotensin I.

Although ACEIs and ARBs both target the renin system and are treated by clinicians as being equivalent, this may not be appropriate. While both drug classes reduce the downstream effects of angiotensin II, it is not clear that these medications are in fact clinically equivalent. ACEIs, for example, do not entirely block production of angiotensin II because of the presence of unaffected converting enzymes. Also, ACEIs have well-known side effects not shared by ARBs, including cough (estimated incidence 5 to 20 percent) and angioedema (estimated incidence 0.1 to 0.2 percent, with a lesser reported risk with ARBs). Additional considerations arise with the newer direct renin inhibitors, because their side-effect profiles and efficacy may differ significantly from ACEIs or ARBs. Given the public health importance and widespread use of these agents, it is important to understand their comparative effects on clinical outcomes.

This review summarizes the evidence on the comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors, focusing on their use for treating essential hypertension in adults. It is an update of a 2007 report that evaluated the scientific literature on ACEIs and ARBs for adults with essential hypertension and adds an evaluation of direct renin inhibitors, which were not covered in the original report. The need for this updated report was determined by an analysis conducted by the Southern California Evidence-based Practice Center. In that analysis, investigators assessed the conclusions from the original comparative effectiveness review, performed a limited literature search of potentially new evidence, and solicited expert opinions concerning the state of the evidence and validity of the original report.

Key Questions addressed are:

Key Question 1. For adult patients[a] with essential hypertension, how do ACEIs (angiotensin-converting enzyme inhibitors), ARBs (angiotensin II receptor antagonists), and direct renin inhibitors[b] differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes[c]?

Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety,[d] adverse events,[e] tolerability, persistence with drug therapy, and treatment adherence?

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[a]"Adult patients" are defined as adults, age 18 years or older.

[b]ACEIs evaluated are: Benazepril (Lotensin), captopril (Capoten), enalapril (Vasotec), fosinopril (Monopril), lisinopril (Prinivil, Zestril), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), ramipril (Altace), and trandolapril (Mavik). ARBs considered are: Candesartan cilexetil (Atacand), eprosartan (Teveten), irbesartan (Avapro), losartan (Cozaar), olmesartan medoxomil (Benicar), telmisartan (Micardis), and valsartan (Diovan). Direct renin inhibitors considered are: Aliskiren (Tekturna).

[c]Outcomes considered include:

Primary outcomes:

1. Blood pressure control (we will prefer seated trough blood pressure, where reported).
2. Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific).
3. Morbidity (especially major cardiovascular events [myocardial infarction (MI), stroke] and measures of quality of life).
4. Safety (focusing on serious adverse event rates, overall adverse event rates, and withdrawals due to adverse events, withdrawal rates, and switch rates).
5. Specific adverse events (including, but not limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia).
6. Persistence/adherence.
7. Rate of use of a single antihypertensive medication for blood pressure control.

Secondary outcomes:

1. Lipid levels (high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglycerides).
2. Rates of progression to type 2 diabetes.
3. Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], dosage of insulin or other diabetes medication, fasting plasma glucose, or aggregated measures of serial glucose measurements).
4. Measures of left ventricular mass/function (left ventricular mass index and ejection fraction).
5. Measures of kidney disease (creatinine/glomerular filtration rate [GFR], proteinuria)

[d]Safety outcomes considered include: Overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, and switch rates. (For practical reasons, we separate safety/adverse events and tolerability/persistence [including switch rates], as the latter may or may not be due to identifiable adverse events.)

Key Question 3. Are there subgroups of patients—based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications)—for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?

Conclusions

Table A provides an aggregated view of the strength of evidence and brief conclusions from this review of the comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for adults with essential hypertension.

Table A. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for adults with essential hypertension

Key Question	Strength of Evidence	Conclusions
Key Question 1. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in the following health outcomes:		
a. Blood pressure control?	High (ACEI vs. ARB); Low (DRI vs. ACEI or ARB)	ACEIs and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. This conclusion is based on evidence from 77 studies (70 RCTs, 5 nonrandomized controlled clinical trials, 1 retrospective cohort study, and 1 case-control study) in which 26,170 patients receiving an ACEI or an ARB were followed for periods from 12 weeks to 5 years (median 24 weeks). Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols. Evidence concerning the effect of direct renin inhibitors on blood pressure is very limited and currently based on only three studies. These studies found the direct renin inhibitor to have a greater reduction in blood pressure compared to the ACEI ramipril (two studies) and no significant difference compared to the ARB losartan (one study).

[e]Specific adverse events: These included, but were no limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia.

Table A. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for adults with essential hypertension (continued)

Key Question	Strength of Evidence	Conclusions
b. Mortality and major cardiovascular events?	Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	Due to low numbers of deaths or major cardiovascular events reported, it was difficult to discern any differential effect of ACEIs versus ARBs versus direct renin inhibitors with any certainty for these critical outcomes. In 21 studies that reported mortality, MI, or clinical stroke as outcomes among 38,589 subjects, 38 deaths and 13 strokes were reported. This may reflect low event rates among otherwise healthy patients and relatively few studies with extended followup. Only 3 of these 21 studies (including 1 death) evaluated direct renin inhibitors versus ACEIs or ARBs, and therefore the evidence to discern any differential effects between these drug classes on mortality and major cardiovascular events was insufficient.
c. Quality of life?	Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	No differences were found between ACEIs and ARBs in measures of general quality of life; this is based on four studies, two of which did not provide quantitative data. No study evaluated the comparative effectiveness of direct renin inhibitors for quality-of-life outcomes.
d. Rate of use of a single antihypertensive medication?	High (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	There was no statistically evident difference in the rate of treatment success based on use of a single antihypertensive for ARBs compared to ACEIs. The trend toward less frequent addition of a second agent to an ARB was heavily influenced by retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients, and by RCTs with very loosely defined protocols for medication titration and switching. There were no relevant studies evaluating direct renin inhibitors.

Table A. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for adults with essential hypertension (continued)

Key Question	Strength of Evidence	Conclusions
e. Risk factor reduction and other intermediate outcomes?	Lipid levels, markers of carbohydrate metabolism/ diabetes control, progression of renal disease: Moderate (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	There were no consistent differential effects of ACEIs, ARBs, on several potentially important clinical outcomes, including lipid levels and markers of carbohydrate metabolism/diabetes control. There appears to be a small difference in change in renal function between ACEIs and ARBs (favoring ACEIs), but this difference is both small and most likely not clinically meaningful or significant. Relatively few studies assessed these outcomes over the long term. There were no studies that evaluated these outcomes in direct renin inhibitors.
	Progression to type 2 diabetes and LV mass/function: Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	There was no evidence for an impact of ACEIs, ARBs, or direct renin inhibitors on glucose or A1c, and no included studies evaluated rates of progression to type 2 diabetes mellitus. Although we included 13 studies of LV mass/function, these were dominated by poor-quality studies with small sample sizes, and only one study included evaluation of a direct renin inhibitor.

Table A. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for adults with essential hypertension (continued)

Key Question	Strength of Evidence	Conclusions
Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?	Cough: High (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	ACEIs have been consistently shown to be associated with greater risk of cough than ARBs (odds ratio 0.211; 95% CI 0.159 to 0.281). For RCTs, this translates to a difference in rates of cough of 7.8 percent; however, for cohort studies with lower rates of cough, this translates to a difference of 1.2 percent. There were only two studies comparing direct renin inhibitors to ACEIs and these gave an estimated odds ratio of 0.333 (95% CI of 0.2241 to 0.4933).
	Withdrawals due to adverse events: High (ACEI vs. ARB); Low (DRI vs. ACEI or ARB)	The withdrawal rate for ARBs was found to have an estimated odds ratio of 0.565 (95% CI 0.453 to 0.704) compared with ACEIs. For RCTs, this translated to an absolute difference in withdrawals of 2.3 percent (5.4% versus 3.1%). The direct renin inhibitor trials did not find a statistically significant difference (odds ratio 0.886; 95% CI 0.458 to 1.714) when compared with the withdrawal rate associated with ACEIs. There was no evidence of differences across treatments in rates of other commonly reported specific adverse events.
	Angioedema: Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	Although several studies collected data on angioedema, the event rates were very low or zero for all studies; this limited our ability to accurately characterize the frequency of angioedema. In the four studies that did report episodes of angioedema, this adverse event was observed only in patients treated with an ACEI (five patients from three studies) or a direct renin inhibitor (one patient in one study).
	Persistence with drug therapy/ treatment adherence: Moderate (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	ACEIs and ARBs have similar rates of treatment adherence based on pill counts; this result may not be applicable outside the clinical trial setting. Rates of continuation with therapy appear to be somewhat better with ARBs than with ACEIs; however, due to variability in definitions, limitations inherent in longitudinal cohort studies, and relatively small sample sizes for ARBs, the precise magnitude of this effect is difficult to quantify. The three included studies evaluating direct renin inhibitors did not find evidence of differences in treatment adherence compared with ACEIs or ARBs. Persistence was not evaluated in any of the studies including direct renin inhibitors.
Key Question 3. Are there subgroups of patients—based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications)—for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?	Insufficient (ACEI vs. ARB; DRI vs. ACEI or ARB)	Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs, ARBs, and direct renin inhibitors for any particular patient subgroup.

ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CI = confidence interval; GFR = glomerular filtration rate; LV = left ventricular; MI = myocardial infarction; RCTs = randomized controlled trials

Remaining Issues

Despite the importance of both ACEIs and ARBs for treatment of essential hypertension, there is little comparative evidence for long-term benefits and harms of these two classes of agents. In particular, there is a lack of information about death or major cardiovascular events, and inconsistently reported data on adverse events. Only nine studies compared ACEIs and ARBs for periods longer than 1 year. In addition, although direct renin inhibitors have been proposed as a new class with potentially more favorable side-effect profiles and efficacy, the number of studies with comparative evidence for this new drug class versus ACEIs or ARBS is extremely limited. Only three studies focusing on direct renin inhibitors met our inclusion criteria, with the longest followup being 36 weeks.

Future Research

With the exception of rates of cough, the hypothesis that ACEIs, ARBs, and direct renin inhibitors have clinically meaningful differences in long-term outcomes in individuals with essential hypertension is not strongly supported by the available evidence. Given the importance of these issues, it is notable how few large, long-term, head-to-head studies have been published.

Further comparative studies in this area should emphasize:

- Subgroups of special importance such as individuals with essential hypertension and diabetes mellitus, congestive heart failure, chronic kidney disease, and dyslipidemia.
- Pragmatic designs such as clinical trials in which treatment is consistent with typical clinical practice, or randomization by organizationally meaningful clusters such as practice organizations or health plans.
- Outcomes over several years.
- Outcomes measured according to current clinical standards.
- Broader representation of groups such as the elderly and ethnic and racial minorities.
- Evaluation of specific pairs of ACEIs and ARBs to allow differentiation within class. (Only one direct renin inhibitor, aliskiren, is currently available.)
- Long-term comparisons of direct renin inhibitors with ACEIs and ARBs.

In addition, we think that research aimed at generating additional evidence regarding four specific areas should be prioritized. These areas include:

1. The incidence, timing, and clinical consequences of angioedema in patients treated with ACEIs, ARBs, or direct renin inhibitors.
   Comment: Angioedema is a well-known adverse reaction to ACEIs and ARBs; however, due to its infrequent occurrence, we lacked sufficient evidence to directly compare the incidence, timing, and clinical consequences of this reaction among patients treated with ACEIs, ARBs, or direct renin inhibitors. Others have estimated that angioedema is experienced by 1 in every 1,000 patients treated with an ACEI, and 1 to 5 of every 10,000 of those treated with an ARB. Furthermore, others have reported a three- to fourfold increased risk of angioedema in African-American patients treated with an ACEI versus Caucasian patients treated with an ACEI. Future research should utilize large databases with sufficient sample sizes to obtain more precise estimates of this rare but serious event. Assessment of study designs or analyses that could explore the impact of angioedema should be prioritized.

2. Relative persistence with drug therapy across the different classes of drugs.
   Comment: Although we report with moderate confidence that persistence with drug therapy is greater with ARB treatment than with ACEI treatment, medication discontinuation rates varied significantly across studies. Because medication discontinuation often requires followup visits and initiation of alternative medications, it has important health economic implications. Future studies that more precisely estimate discontinuation rates in usual clinic settings, the additional health care utilization following discontinuation, and the conditional tolerability of an ACEI or ARB following prior intolerance to one of these agents would be valuable in understanding the consequences of differential medication discontinuation.
3. The impact of cough on patients' quality of life.
   Comment: Given the demonstrated higher incidence of cough with ACEIs, it would also be valuable to gain more precise understanding of the impact of cough on quality of life, care patterns (e.g., use of therapeutic agents for cough symptoms or conditions associated with cough), and health outcomes, particularly for individuals who continue to use ACEIs.
4. The potential to gain insight on the comparative benefits and harms of ACEIs, ARBs, and direct renin inhibitors based on findings from studies evaluating patients with other, related conditions such as congestive heart failure, ischemic heart disease, and chronic kidney disease.
   Comment: While our review is restricted to patients with essential hypertension, the agents studied here have been compared in large studies for related conditions such as congestive heart failure, ischemic heart disease, and chronic kidney disease. Trials comparing ACEIs, ARBs, and direct renin inhibitors in these target conditions often report the outcomes of interest in this review. For evaluation of rarer events (e.g., mortality or angioedema) it may be worth combining data across target conditions. Future research should consider this strategy and evaluate the extent to which results differ across target conditions.

Introduction

Background

Almost 75 million American adults—approximately one-third—have hypertension. The prevalence of hypertension increases with advancing age such that more than half of people 55 to 74 years old and approximately three-fourths of those age 75 years and older are affected.[1] In addition to being the primary attributable risk factor for death throughout the world,[2] hypertension results in substantial morbidity because of its impact on numerous target organs, including the brain, eyes, heart, arteries, and kidneys.

Despite the high morbidity and mortality attributable to hypertension and recent improvements in hypertension treatment, control of the condition remains suboptimal. Approximately one-quarter of adults remain unaware of their hypertension, one-third of individuals with hypertension are not on treatment, and one-half of hypertensive patients continue to have blood pressure above even modest treatment goals (< 140/90 mmHg).[3] Several nonpharmacological interventions—including diet, exercise, and control of body weight—are effective in lowering blood pressure; however, such therapies are often insufficient or not sustained, resulting in reliance on pharmacotherapy. Various classes of antihypertensive drug treatments are available, but determining their comparative effectiveness is complicated. Therapeutic choices may be influenced by patient characteristics—including comorbidities and race—that also affect the risk of certain clinical end points. Multidrug therapy is often required to achieve satisfactory control, leading to greater variables to consider in treatment choices.[4] Finally, adverse events that are characteristic of the individual agents or drug classes further complicate therapeutic decisionmaking.

Among the many choices in antihypertensive therapy, some of the most common are those aimed at affecting the renin-angiotensin-aldosterone (renin) system. The renin system is an important mediator of blood volume, arterial pressure, and cardiac and vascular function. Components of this system can be identified in many tissues, but the primary site of renin release is the kidney. The renin system can be triggered by sympathetic stimulation, renal artery hypotension, and decreased sodium delivery to the distal tubule. Through proteolytic cleavage, renin acts on the oligopeptide substrate angiotensinogen to produce the decapeptide angiotensin I. In turn, two terminal peptide residues of angiotensin I are removed by the angiotensin-converting enzyme (ACE) to form the octapeptide angiotensin II. Angiotensin II acts directly on the resistance vessels to: increase systemic vascular resistance and arterial pressure; stimulate the adrenal cortex to release aldosterone, which leads to increased sodium and water reabsorption and potassium excretion; promote secretion of antidiuretic hormone, which leads to fluid retention; stimulate thirst; promote adrenergic function; and increase cardiac and vascular hypertrophy.

Therapies aimed at modifying the renin system have been used extensively for treatment of hypertension, heart failure, myocardial infarction (MI), diabetes, and renal disease.[5,6] Currently, three classes of drugs that interact with this system are used to inhibit the effects of angiotensin II: the angiotensin-converting enzyme inhibitors (ACEIs); the angiotensin II receptor antagonists (ARBs); and the direct renin inhibitors. ACEIs block the conversion of angiotensin I into angiotensin II; ARBs selectively inhibit angiotensin II from activating the angiotensin specific receptor (AT_1); and direct renin inhibitors block the conversion of angiotensinogen into angiotensin I.

Although ACEIs, ARBs, and direct renin inhibitors all target the renin system and are often treated by clinicians as being equivalent, this may not be appropriate. While all three drug classes reduce the downstream effects of angiotensin II, there are differences that may distinguish them. ACEIs, for example, do not entirely block production of angiotensin II because of the presence of unaffected converting enzymes. Treatment with an ACEI, but not an ARB, results in increased levels of bradykinin, and this mechanism may mediate differences in clinical efficacy or side effects such as cough or angioedema. Unlike ACEIs and direct renin inhibitors, ARBs selectively block the effects of angiotensin II at the AT_1 receptor. Both ACEIs and ARBs result in compensatory increases in plasma renin activity, an effect not shared by direct renin inhibitors.[7] ACEIs have well-known side effects not shared by ARBs, including cough (estimated incidence 5 to 20 percent) and angioedema (estimated incidence 0.1 to 0.2 percent, with a lesser reported risk with ARBs).[8] Although ACEIs, ARBs and direct renin inhibitors are highly effective in lowering blood pressure among patients with essential hypertension,[5,6] the comparative effectiveness of these medication classes is not known. ACEIs and ARBs are the second and fifth most commonly prescribed medications for hypertension, respectively, and the use of direct renin inhibitors has been rising since their introduction.[9] Although ACEIs and ARBs are occasionally used in combination, such combinations provide little blood pressure lowering over each agent used alone,[10] and are associated with increased adverse events.[11] As a result, most providers choose to use either an ACEI or an ARB for hypertension. It is therefore important to understand the comparative effectiveness of these agents for providers making this choice.

In this comparative effectiveness review, which updates the 2007 report Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension,[12] we examine the scientific literature on ACEIs, ARBs, and direct renin inhibitors for individuals with hypertension. The outcomes analyzed in this comparison are the relative benefits (i.e., blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes), as well as safety (i.e., adverse events, tolerability, persistence with drug therapy, and treatment adherence). Moreover, we examine the clinical determinants of these outcomes, such as age, race, ethnicity, sex, comorbidities, and concurrent use of other medications. The focus is on long-term outcomes and impact.

The need for this updated report was determined by an analysis conducted by the Southern California Evidence-based Practice Center.[13] In that analysis, investigators assessed the conclusions from the original comparative effectiveness review, performed a limited literature search of potentially new evidence, and solicited expert opinions concerning the state of the evidence and validity of the original report.

Scope and Key Questions

This review summarizes the evidence on the comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for treating essential hypertension in adults. Key Questions addressed are:

Key Question 1. For adult patients[a] with essential hypertension, how do ACEIs (angiotensin-converting enzyme inhibitors), ARBs (angiotensin II receptor antagonists), and direct renin inhibitors[b] differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes[c]?

Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety,[d] adverse events,[e] tolerability, persistence with drug therapy, and treatment adherence?

Key Question 3. Are there subgroups of patients—based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications)—for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?

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[a]"Adult patients" are defined as adults, age 18 years or older.

[b]Table 1 lists the specific ACEIs, ARBs, and direct renin inhibitors evaluated in this review and describes their characteristics and current indications.

[c]Outcomes considered include:

Primary outcomes:

1. Blood pressure control (we will prefer seated trough blood pressure, where reported).
2. Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific).
3. Morbidity (especially major cardiovascular events [myocardial infarction (MI), stroke] and measures of quality of life).
4. Safety (focusing on serious adverse event rates, overall adverse event rates, and withdrawals due to adverse events, withdrawal rates, and switch rates).
5. Specific adverse events (including, but not limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia).
6. Persistence/adherence.
7. Rate of use of a single antihypertensive medication for blood pressure control.

Secondary outcomes:

1. Lipid levels (high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglycerides).
2. Rates of progression to type 2 diabetes.
3. Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], dosage of insulin or other diabetes medication, fasting plasma glucose, or aggregated measures of serial glucose measurements).
4. Measures of left ventricular mass/function (left ventricular mass index and ejection fraction).
5. Measures of kidney disease (creatinine/glomerular filtration rate [GFR], proteinuria).

[d]Safety outcomes considered include: Overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, and switch rates. (For practical reasons, we separate safety/adverse events and tolerability/persistence [including switch rates], as the latter may or may not be due to identifiable adverse events.)

[e]Specific adverse events: These included, but were no limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
ACEIs				
Benazepril (Lotensin)	- After oral administration, peak plasma concentrations reached within 0.5–1 hr. - Effective half-life in adults following multiple dosing 10–12 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	Treatment of hypertension. May be used alone or in combination with thiazide diuretics.	Initial dose for adults not receiving a diuretic is 10 mg once daily. Usual maintenance range is 20–40 mg per day in a single or two equal doses.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - In patients with renal insufficiency (creatinine clearance ≤30 mL/min/1.73 m^2) peak levels and initial half-life increase, time to steady state may be delayed. Recommended initial dose in such patients is 5 mg once daily. Dosage may be titrated upward until BP is controlled or to a maximum total daily dose of 40 mg.
Captopril (Capoten)	- After oral administration, peak plasma concentrations reached in 1 hr. Presence of food reduces absorption by 30–40%. - In adults, effective half-life < 3 hr (accurate determination of half-life not possible). - In a 24–hr period, 95% of observed dose eliminated in the urine. - Reduction of BP maximum at 60–90 minutes after oral administration, duration of effect dose-related. - Reduction in BP may be progressive.	1. Treatment of hypertension. 2. Treatment of congestive heart failure. 3. To improve survival following MI in clinically stable patients.	Should be taken 1 hr before meals, dosage must be individualized. Initial dose is 25 mg twice per day or three times per day. Dosage may be increased to 50 mg twice per day or three times per day. Usual dose range is 25–150 mg twice per day or three times per day.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment: initial daily dose should be reduced, smaller increments should be utilized for titration, and minimal effective dose should be calculated.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Enalapril (Vasotec)	- After oral administration, peak serum concentrations occur within 1 hr. - Primarily renal, 94% of dose is recovered in the urine and feces. - Effective half-life following multiple doses is 11 hr. - With GFR ≤ 30 mL/min, time to peak concentration and steady state delayed.	Treatment of hypertension.	10–40 mg per day in a single or two divided doses. Daily dose should not exceed 50 mg. Dosage reduction and/or discontinuation may be required for some patients who develop increases in blood urea and serum creatinine.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. Enalapril has been detected in human breast milk. - Dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range.
Fosinopril (Monopril)	- After oral administration, peak concentrations achieved in 3 hr. - Terminal elimination half-life is 12 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or with thiazide diuretics. 2. For heart failure as adjunctive therapy when added to conventional therapy, including diuretics with or without digitalis.	Initial dosage is 10 mg once daily, both as monotherapy and when the drug is added to a diuretic.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - In children, doses between 0.1 and 0.6 mg/kg. For children weighing more than 50 kg, dosage is 5–10 mg once daily. - For heart failure patients, an initial dose of 5 mg can be increased over a several-week period but not exceeding 40 mg once daily.
Lisinopril (Prinivil; Zestril)	- Reaches peak serum concentrations within 7 hr. - On multiple doses, effective half-life accumulation is 12 hr. - Excreted primarily through the kidneys.	1. Treatment of hypertension. 2. As adjunctive therapy in the management of heart failure not responding to diuretics and digitalis. 3. Acute MI – for the treatment of hemodynamically stable patients, to improve survival.	Initial dose is 10 mg once daily, usual dose range 20–40 mg daily in a single dose. Patients on a diuretic dosage should be adjusted according to BP response, and the diuretic should ideally be discontinued. For patients with creatinine clearance ≤ 10 mL/min, recommended initial dose is 2.5 mg, can be titrated upward up to a maximum of 40 mg daily.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Dose selection for elderly patients should start at the low end of dosing range.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Moexipril (Univasc)	- Bioavailability of oral drug is 13% compared to IV; markedly affected by food. - After oral administration, 7% appears in urine (vs. 40% of IV dose), 52% in feces (vs. 20% of IV dose).	Treatment of hypertension.	Initial dose in patients not receiving diuretics is 7.5 mg 1 hr prior to meals, once daily. Recommended dose range is 7.5–30 mg daily in one or two divided doses. Diuretic therapy should ideally be discontinued or an initial dose of 3.75 mg should be used with medical supervision. For patients with creatinine clearance ≤ 40 mL/min/1.73 m^2, the recommended initial dose is 3.75 mg once daily, can be titrated to a maximum daily dose of 15 mg.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Dosage should be adjusted for populations with decreased renal function, mild to moderate cirrhosis and in elderly patients.
Perindopril (Aceon)	- After oral administration, peak plasma concentrations occur at approximately 1 hr. - Mean half-life 0.8–1.0 hr. - Clearance almost exclusively renal.	1. Treatment of hypertension. May be used alone or in combination with thiazide diuretics. 2. Stable coronary artery disease: to reduce risk of cardiovascular mortality or nonfatal MI.	Initial dose is 4 mg once daily. May be titrated upward until BP is controlled to a maximum of 16 mg per day. Usual dose range is 4–8 mg as single daily dose. May be given in two divided doses.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Dose selection for elderly patients should start at the low end of dosing range. - Patients with renal impairment: initial daily dose should be reduced.
Quinapril (Accupril)	- After oral administration, peak plasma concentrations reached within 1 hr. - After multiple oral dosing, effective half-life within 2 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or with thiazide diuretics. 2. Management of heart failure as adjunctive therapy when added to conventional therapy, including diuretics and/or digitalis.	Initial dosage for patients not on diuretics is 10–20 mg once daily. Dosage adjusted according to BP measured at peak and trough.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment and heart failure: initial daily dose should be reduced. - Recommended dosage for elderly patients is 10 mg once daily followed by titration to the optimal response.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Ramipril (Altace)	- After oral administration, peak plasma concentrations reached within 1 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or in combination with thiazide diuretics. 2. Reduction in risk of MI, stroke, and death from cardiovascular causes for patients 55 years or older at high cardiovascular risk.	Initial dose for patients not receiving a diuretic is 2.5 mg once daily. Dosage adjustment according to BP response. Usual maintenance dosage is 2.5–20 mg once daily in a single dose or divided equally into two doses.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment: initial daily dose should be reduced, smaller increments should be utilized for titration and minimal effective dose should be calculated.
Trandolapril (Mavik)	- After oral administration under fasting conditions, peak concentrations occur within 1 hr. - Effective half-life approximately 6 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or with other antihypertensive medication. 2. Heart failure post-MI or LV dysfunction post-MI. Used to decrease risk of death and heart failure-related hospitalization.	Initial dosage in patients not receiving a diuretic is 1 mg once daily in patients who are not black and 2 mg in black patients. Dosage adjusted according to BP.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment: initial daily dose should be reduced, smaller increments should be utilized for titration and minimal effective dose should be calculated.
ARBs				
Candesartan cilexetil (Atacand)	After oral administration, peak serum concentrations reached after 3–4 hr. - Elimination of half-life is approximately 9 hr. - Excreted in urine and feces.	1. Treatment of hypertension. May be used alone or in combination with other antihypertensive agents. 2. Heart failure: used in patients with LV systolic dysfunction to reduce risk of cardiovascular death and heart failure hospitalization.	Initial dose is 16 mg once daily. Can be given once or twice daily with doses ranging from 8–32 mg. Effect is usually present within 2 weeks, and maximal BP reduction occurs within 4–6 weeks.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the renin angiotensin system can cause injury and even death to the developing fetus. - Lower dose for patients with moderate hepatic impairment or depletion of intravascular volume.
Eprosartan (Teveten)	- After oral administration, plasma concentrations peak around 1–2 hr in the fasted state. - Mean terminal elimination half-life following multiple doses of 600 mg was 20 hr. - Eliminated primarily by biliary and renal excretion.	Treatment of hypertension. May be used alone or in combination with other antihypertensives, such as diuretics and calcium channel blockers.	Initial dose is 600 mg once daily. Can be given once or twice daily with doses ranging 400 mg to 800 mg.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Elderly, hepatically impaired, or renally impaired patients should not exceed 600 mg daily.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Irbesartan (Avapro)	- After oral administration, peak plasma concentrations reached at 1.5–2 hr. - Average terminal elimination of half-life is 11–15 hr. - Eliminated primarily by biliary and renal excretion.	1. Treatment of hypertension. May be used alone or with other antihypertensive agents. 2. Nephropathy in type 2 diabetic patients. Indicated for treatment of patients with an elevated serum creatinine and proteinuria > 300 mg/day). Reduces rate of progression of nephropathy.	Initial dose is 150 mg once daily. Patients who require more reduction in BP should be titrated to 300 mg once daily.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Nephropathy in type 2 diabetic patients: maintenance dose is 300 mg once daily. - Children (6–12 years): initial dose of 75 mg, up to 150 mg once daily. Ages 13–16: initial 150 mg once daily, can be titrated to 300 mg once daily, higher doses not recommended. - Lower initial dose for patients with depletion of intravascular volume or salt.
Losartan (Cozaar)	- After oral administration, mean peak concentrations reached in 1 hr. - Terminal half-life is 2 hr. - Eliminated primarily by biliary and renal excretion.	1. Treatment of hypertension. May be used alone or with other antihypertensive agents, including diuretics. 2. Hypertensive patients with LV hypertrophy: reduces risk of stroke, though some evidence that this does not apply to black patients. 3. Nephropathy in type 2 diabetic patients: reduces rate of progression of nephropathy as measured by doubling of serum creatinine or end-stage renal disease.	Initial dose is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume and patients with history of hepatic impairment. May be given twice daily with total doses from 25 mg to 100 mg.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Pediatric hypertensive patients (6 years and greater): starting dose is 0.7 mg/kg once daily (up to 50 mg total) given as tablet or a suspension. - Hypertensive patients with LV hypertrophy: starting dose is 50 mg once daily. Based on BP response, hydrochlorothiazide 12.5 mg daily should be added and/or dose of losartan should be increased to 100 mg once daily followed by an increase of hydrochlorothiazide to 25 mg once daily.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Olmesartan medoxomil (Benicar)	- After oral administration, peak plasma concentrations reached after 1–2 hr. - Terminal elimination of half-life is 13 hr. - Eliminated primarily by biliary and renal excretion.	Treatment of hypertension. May be used alone or with other antihypertensive agents.	Initial dose is 20 mg once daily. For patients requiring further reduction in BP, dose may be increased to 40 mg.	When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - In patients with impaired renal failure, a lower starting dose should be considered.
Telmisartan (Micardis)	- After oral administration, peak concentrations reached within 0.5–1 hr. - Terminal elimination of half-life is 24 hr. - Eliminated mostly through feces.	Treatment of hypertension. May be used alone or with other antihypertensive agents.	Starting dose is 40 mg once daily. BP response is dose-related over range of 20–80 mg.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Patients with depletion of intravascular volume, biliary obstructive disorders, or hepatic insufficiency should start treatment under close medical supervision.
Valsartan (Diovan)	- After oral administration, peak plasma concentrations reached within 2–4 hr. - Average elimination half-life about 6 hr. - Primarily eliminated in feces and urine.	1. Treatment of hypertension. May be used alone or with other antihypertensive agents. 2. Heart failure: used in treatment of heart failure, reduces hospitalizations. 3. Post-MI: used to reduce cardiovascular mortality.	Initial dose is 80 mg or 160 mg once daily in patients who are not volume depleted. May be used over a dose range of 80 mg to 320 mg once daily.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Care should be given when dosing patients with hepatic or severe renal impairment.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Direct renin inhibitor				
Aliskiren (Tekturna)	- Poorly absorbed (bioavailability about 2.5%) with an approximate accumulation half-life of 24 hours. - Steady state blood levels are reached in about 7–8 days. - Following oral administration, peak plasma concentrations of aliskiren are reached within 1–3 hr. - When taken with a high-fat meal, mean AUC and Cmax of aliskiren are decreased by 71% and 85% respectively. - One-fourth of the absorbed dose appears in the urine as parent drug.	Treatment of hypertension.	- May be used alone or in combination with other antihypertensive agents. - Use with maximal doses of ACEIs has not been adequately studied. - Starting dose: 150 mg once daily. - If blood pressure remains uncontrolled titrate up to 300 mg (available in 150 mg and 300 mg. tablets). - Patients should establish a routine pattern for taking aliskiren with regard to meals. High-fat meals decrease absorption substantially.	- No adjustment of the starting dose is required in elderly patients, patients with mild-to-severe renal impairment or mild to- severe hepatic insufficiency. - Care should be taken when dosing aliskiren in patients with severe renal impairment, as clinical experience with such patients is limited. - Pediatric patients: The pharmacokinetics of aliskiren have not been investigated in patients < 18 years of age. - Nursing mothers: It is not known whether aliskiren is excreted in human breast milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. - Race: The pharmacokinetic differences between blacks, Caucasians, and the Japanese are minimal.

ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor antagonist(s); BP = blood pressure; GFR = glomerular filtration rate; hr = hour(s); LV = left ventricular; MI = myocardial infarction

Methods

Topic Development

The topic for the original 2007 report[12] was nominated in a public process. With input from technical experts, the Scientific Resource Center (SRC) for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program drafted the initial Key Questions for that report and, after approval from AHRQ, posted them to a public Web site. The public was invited to comment on these questions. After reviewing the public commentary, the SRC drafted final Key Questions and submitted them to AHRQ for approval.

For the present updated report, AHRQ initially proposed the same scope and Key Questions. In response to input from the project's technical expert panel, the Key Questions were modified to include the comparative risks and benefits of direct renin inhibitors. The revised Key Questions were then posted to a public Web site for comment and were modified again in response to the comments received.

Search Strategy

We conducted a comprehensive search of the scientific literature to identify systematic reviews, randomized controlled trials, and nonrandomized comparative studies relevant to the Key Questions. Searches of electronic databases used the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for MEDLINE and adapted for use in other databases. Searches included terms for drug interventions, hypertension, and study design, and were limited to studies published in English after 1988. The texts of the major search strategies are given in Appendix A. We also reviewed selected gray literature (e.g., regulatory data, clinical trial registries and conference abstracts) received from the SRC, the reference lists of relevant review articles, and citations identified by peer and public reviewers of the draft report. Gray literature is defined as "that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers."[14] We did not undertake a systematic search for unpublished data.

To identify literature describing direct comparisons of angiotensin-converting enzyme inhibitor(s) (ACEIs), angiotensin II receptor blocker(s)/antagonist(s) (ARBs), or direct renin inhibitors we searched:

- MEDLINE (1966 to December 23, 2010);
- Embase (all years, ending on December 23, 2010);
- The Cochrane Central Register of Controlled Trials (Issue 2, 2006; not updated thereafter);
- A register of systematic reviews underway in the Cochrane Hypertension Review Group (December 1, 2010); and
- Gray literature identified by the SRC (last search date December 30, 2009).

Table 2 lists the types and sources of gray literature searched by the SRC:

Table 2. Types and sources of gray literature searched

Type of source	Specific sources searched
Regulatory information	FDA Health Canada Authorized Medicines for EU
Clinical trial registries	ClinicalTrials.gov Current Controlled Trials Clinical Study Results WHO Clinical Trials
Abstracts and conference papers	Conference Papers Index Scopus
Grants and federally funded research	NIH RePORTER (a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions) HSRPROJ (a database providing access to ongoing grants and contracts in health services research)
Other miscellaneous sources	Hayes, Inc. Health Technology Assessment NY Academy of Medicine's Grey Literature Index

EU = European Union; FDA = U.S. Food and Drug Administration; NIH = National Institutes of Health; NY = New York; WHO = World Health Organization

In our original report, we conducted additional searches in MEDLINE for studies of ARBs versus other (non-ACEI) comparators and ACEIs versus other (non-ARB) comparators for potential use in the event that evidence from direct head-to-head trials proved to be insufficient for some or all of the outcomes of interest in the review. The process used to screen this literature and evaluate its relevance is described in Appendix B. Because we did not use the evidence from these indirect comparisons in our original report, we eliminated this step in the current update and did not search for or include such indirect comparison studies.

Our searches identified a total of 2090 citations. We imported all citations into an electronic database (EndNote version X4).

Study Selection

We developed criteria for inclusion and exclusion based on the patient populations, interventions, and outcome measures specified in the Key Questions. The abstract screening criteria we used (Appendix C) were designed to identify only relevant direct head-to-head comparator studies (ACEIs vs. ARBs, ACEIs vs. direct renin inhibitors, or ARBs vs. direct renin inhibitors). We retrieved the full text of all potentially relevant articles for further review. We then applied a second, more stringent set of criteria for inclusion and exclusion (Appendix C).

The remainder of this section describes in greater detail the criteria we used to screen the available literature.

Population and Condition of Interest

As specified in the Key Questions, this review focused on adult patients (age 18 years or older) with essential hypertension, as defined by study authors. We included studies with patients of mixed ages and mixed diagnoses only if results were reported separately for the relevant subgroups.

Interventions and Comparators of Interest

We included the ACEIs, ARBs, and direct renin inhibitors listed in Table 1. In addition to straightforward comparisons of a single ACEI versus a single ARB or direct renin inhibitor, we also included "grouped" comparisons (e.g., a specific ARB vs. "ACEIs" or unspecified "ARBs" vs. unspecified "ACEIs") and comparisons of an ACEI + drug X versus an ARB + drug X (e.g., losartan + hydrochlorothiazide [HCTZ] versus enalapril + HCTZ). We excluded comparisons of an ACEI + drug X versus an ARB + drug Y (e.g., enalapril + manidipine vs. irbesartan + HCTZ).

Studies with treatment protocols that permitted the addition of other antihypertensive medications during the trial if certain blood pressure targets were not met were included provided the cointervention protocols were the same in both groups.

Outcomes of Interest

We considered a wide range of outcomes pertaining to the long-term benefits and harms of ACEIs, ARBs, or direct renin inhibitors. These are listed above in the section on "Scope and Key Questions." In order of relative priority, these outcomes were:

Primary outcomes:

- Blood pressure control (we preferred seated trough blood pressure, where reported).
- Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific).
- Morbidity (especially major cardiovascular events [myocardial infarction (MI), stroke] and measures of quality of life).
- Safety (focusing on serious adverse event rates, overall adverse event rates, withdrawals due to adverse events, withdrawal rates, and switch rates).
- Specific adverse events (including, but not limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia).
- Persistence/adherence.
- Rate of use of a single antihypertensive medication for blood pressure control.

Secondary outcomes:

- Lipid levels (high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglycerides).
- Rates of progression to type 2 diabetes.
- Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], dosage of insulin or other diabetes medication, fasting plasma glucose, or aggregated measures of serial glucose measurements).
- Measures of left ventricular mass/function (left ventricular mass index [LVMI] and ejection fraction [LVEF]).
- Measures of kidney disease (creatinine/glomerular filtration rate [GFR], proteinuria).

Timing

The Key Questions ask about the comparative long-term benefits and harms of ACEIs, ARBs, or direct renin inhibitors for treating essential hypertension, but do not define precisely what is meant by "long-term." Some of our outcomes of interest, such as blood pressure lowering or medication side effects, could reasonably be assessed in a short timeframe, while

many others (e.g., persistence, mortality, morbidity) may require years of followup. To include a broad range of studies reporting on our multiple outcomes, we opted to include studies with a minimum of 12 weeks of followup.

Setting

We did not restrict the setting of the studies evaluated in our analysis.

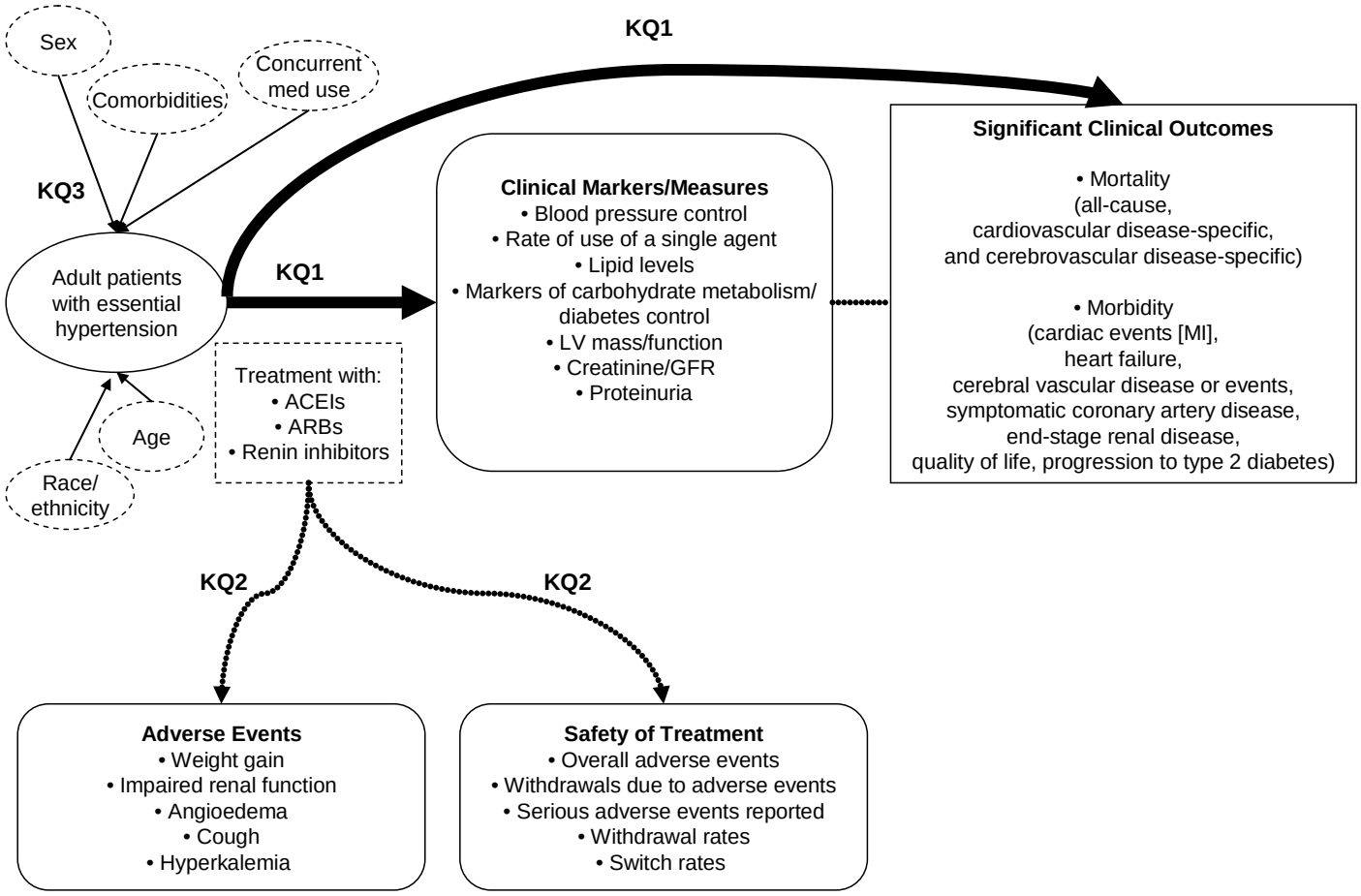
Types of Studies

We included comparative clinical studies of any design, including randomized controlled trials (RCTs), nonrandomized controlled clinical trials, retrospective and prospective cohort studies, and case-control studies.

Analytic Framework

Figure 1 depicts the Key Questions within the context of the population, interventions, comparators of interest, outcomes, timing, and settings (PICOTS) described in the previous section. In general, the figure illustrates how ACEIs, ARBs, and direct renin inhibitors affect (1) measures of blood pressure control, lipid levels, carbohydrate metabolism/diabetes control, measures of LV mass/function, or measures of kidney disease (creatinine/GFR, proteinuria); and/or (2) clinically significant outcomes, such as mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific) or morbidity (especially major cardiovascular events [MI, stroke], rates of progression to type 2 diabetes, and measures of quality of life). In addition, adverse events (including, but not limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia) may occur at any point after ACEIs, ARBs, and/or direct renin inhibitors are received.

Figure 1. Analytic framework



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker(s)/antagonist(s); GFR = creatinine/glomerular filtration rate; LV = left ventricular; MI = myocardial infarction

Data Extraction

We developed a data abstraction form/evidence table template for abstracting data from the included studies (Appendix D) and used the same form for all study designs and to capture data relevant to all three Key Questions. Abstractors worked in pairs: the first abstracted the data, and the second over-read the article and the accompanying abstraction to check for accuracy and completeness. The completed evidence table, including a row for each study, is provided in Appendix E.

We extracted the following data: geographical location; funding source; study design; interventions (including dose, duration, dose titration protocol [if any], and cointerventions [if any]); population characteristics (including age, sex, race/ethnicity, baseline blood pressure, concurrent medications, and comorbidities); recruitment setting; inclusion and exclusion criteria; numbers screened, eligible, enrolled, and lost to followup; and results for each outcome.

Quality Assessment

We used predefined criteria to assess the quality of individual controlled trials and prospective or retrospective observational (cohort) studies. To assess the quality of clinical trials and cohort studies, we adapted criteria developed by the U.S. Preventive Services Task Force (USPSTF) and the Centre for Reviews and Dissemination (CRD).[15,16] The approach used is similar to that now recommended in AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[17]

Individual studies were graded as "good," "fair," or "poor" in quality according to the following definitions:

> A "good" study has the least bias and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
>
> A "fair" study is susceptible to some bias, but probably not sufficient to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
>
> A "poor" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

If a study was rated as fair or poor, assessors were instructed to note important limitations on internal validity based on the USPSTF/CRD criteria, as adapted here:

1. Initial assembly of comparable groups:

   a. For RCTs: Adequate randomization, including concealment and whether potential confounders were distributed equally among groups.
   b. For cohort studies: Consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.
2. Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination).
3. Important differential loss to followup or overall high loss to followup.
4. Measurements: Equal, reliable, and valid (includes masking of outcome assessment).
5. Clear definition of interventions.
6. All important outcomes considered.
7. Analysis: Adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs.

Assessment of each study's quality was made by a single rater and then evaluated by a second rater. Finally, quality assessments were reviewed across studies. Disagreements were resolved by consensus. Final quality assessments for individual studies are included in the evidence table (Appendix E).

Applicability

We did not provide a global rating of applicability (such as "high" or "low") because applicability may differ substantially based on the user of this report. However, applicability of research studies was assessed by noting the most important potential limitations in a study's applicability from among the list described by Rothwell.[18] These criteria, slightly adapted by the SRC for the original 2007 report, are reproduced in Appendix F. Assessors were instructed to list the most important (up to three) limitations affecting applicability, if any, based on this list. The approach used is broadly similar to that now recommended in AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[19]

Throughout this report, we highlight effectiveness studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer followup periods than most efficacy studies. The results of effectiveness studies are more applicable to the spectrum of patients that will use a drug, have a test, or undergo a procedure than results from highly selected populations in efficacy studies.

We chose to include observational designs because these studies may be more likely to reflect the broadest spectrum of patients in typical clinical settings and therefore provide complementary information not adequately captured in clinical trials. Observational studies, however, are prone to significant selection bias and residual confounding and may therefore result in biased estimates of treatment effect. In particular, patients treated with an ARB or direct renin inhibitor may be more likely to have experienced intolerance to an ACEI, or could differ in other important ways associated with cost differences across the medication classes. To address this, we performed separate meta-analyses for RCTs and observational studies so that treatment effects could be estimated without the biases introduced by observational designs.

Rating the Body of Evidence

For the present update, we assessed the strength of the body of evidence for each Key Question using the approach recommended in AHRQ's *Methods Guide for Effectiveness and*

Comparative Effectiveness Reviews.[20] This approach is conceptually similar to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework[21] used in the 2007 report. In rating the strength of evidence, we considered the number of studies, the size of the studies, strength of study design, and the quality of individual studies. We also assessed risk of bias, directness, precision, consistency across studies of the same design, consistency across different study designs, magnitude of effect, applicability, and the potential for publication bias. Finally, if applicable, we considered (especially for observational studies) the potential influence of plausible confounders. We commented specifically when it was difficult or impossible to assess certain of these dimensions. The overall strength of a given body of evidence was rated qualitatively using the following four-level scale:

> High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
>
> Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
>
> Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
>
> Insufficient—Evidence is either unavailable or does not permit estimation of an effect.

Data Synthesis

Given that many studies did not have the statistical power to determine equivalence for the outcomes relevant to this review (which were often not the primary outcomes evaluated by study investigators), we considered synthesis (meta-analysis) in an attempt to overcome the type II error.

In evaluating groups of studies reporting the same or similar outcomes for potential data synthesis, we primarily considered clinical diversity. In this assessment, we tended to be inclusive of individual studies unless their populations were clearly dissimilar (e.g., when considering renal outcomes we chose to exclude from pooled analysis studies of patients with renal failure). We considered groups of studies to be suitable candidates for a quantitative synthesis when we were able to identify at least four clinically relatively similar studies that assessed the same outcome (e.g., when considering effects on lipids, we chose not to pool, as the group included different lipid measures.) While not proof of the validity of this approach, it is notable that there were no situations in which pooled estimates of relative efficacy regarding a particular outcome were contrary to the global impression of the reviewers.

When we calculated summary effect sizes, we stratified these by study design, separating RCTs from observational studies. We used Comprehensive Meta-Analysis Version 2 (Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-Analysis Version 2, Biostat, Englewood NJ [2005]) to synthesize the available evidence. We used Begg's test to assess heterogeneity, while recognizing that the ability of statistical methods to detect heterogeneity is limited, particularly when the number of studies is small. In the presence of statistical heterogeneity, we evaluated study design characteristics to determine whether they could explain the heterogeneity observed. To allow for the presence of statistical heterogeneity, we used

random-effects models. Meta-analyses combining both study designs were also calculated in order to estimate confidence limits for an overall effect.

When meta-analysis was performed, we used the random-effects model for the primary analysis; in addition, we present summary estimates derived using the fixed-effect model as a sensitivity analysis. Furthermore, for dichotomous outcomes, we used the odds ratio as the effect measure. This was done because it resulted in less heterogeneity than did risk differences.

We attempted to conform as closely as possible to the recommendations on performing meta-analyses in AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews.22 We combined dichotomous events using odds ratios and continuous measures using differences in means. Because of the natural heterogeneity of the studies, we primarily reported the results of random-effects models as calculated by Comprehensive Meta-Analysis. We checked for publication bias using funnel plots and Begg and Mazumdar's correlation test for publication bias. We calculated the Q statistic as a measure of heterogeneity, but this was descriptive information, as we expect some heterogeneity in the studies. For reporting the meta-analyses, we attempted to conform as closely as possible to the PRISMA guidelines (www.prisma-statement.org).

Given the dearth of studies of the same ACEI versus ARB comparison and the presumed general similarity of each class, when studies were combined, pooling was performed without regard to the specific drug within the ACEI or ARB class. We stratified the analysis to examine differences between observational studies and RCTs, as described above.

Results

Literature Search and Screening

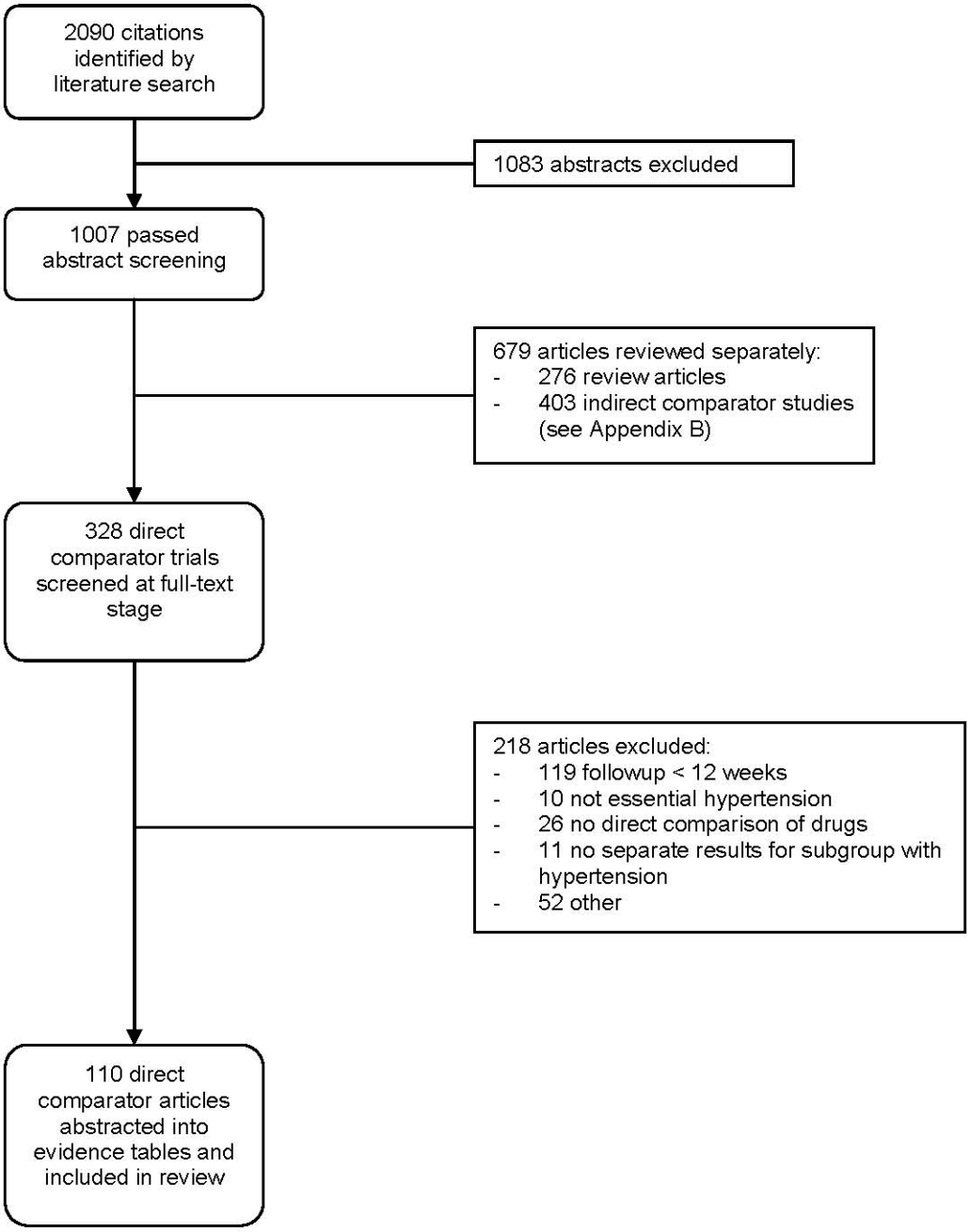
Our searches of the literature identified a total of 2,090 citations. Table 3 details the number of citations identified from each source.

Table 3. Sources of citations

Source	Number of citations
MEDLINE	1,428
Embase	355
Cochrane Central Register of Controlled Trials	45
Register of systematic reviews underway in the Cochrane Hypertension Group	0
References of review articles and primary studies	27
Scientific information packets submitted by pharmaceutical companies	17
Other (recommendations from staff at AHRQ or SRC or from project investigators)	218
Total:	**2,090**

Figure 2 describes the flow of literature through the screening process. Of the 2,090 citations identified by our searches, 1083 were excluded at the abstract screening stage. Of the 1,007 citations that passed the abstract screening, 276 were review or methods articles, 403 were indirect comparator studies identified for our original report (see Appendix B), and 328 were direct comparator studies of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blocker(s)/antagonist(s) (ARBs), and direct renin inhibitors. The remainder of this section describes results for the direct comparator studies.

Figure 2. Literature flow diagram



At the full-text screening stage, 218 of the 328 direct comparator studies were excluded for the reasons summarized in Figure 2, leaving a total of 110 included articles. Appendix G provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

The 110 included direct comparator articles reported on 100 distinct studies. Seventy-four of these were randomized controlled trials (RCTs), 4 were nonrandomized controlled trials, 16 were retrospective cohort studies, 3 were prospective cohort studies, and 1 study each was a cross-sectional cohort, a case-control study, and a retrospective chart review. Table 4 describes the number of studies that evaluated various possible treatment comparisons.

Table 4. Number of studies (number of publications) that evaluated various treatment comparisons*

		ARBs								DRI	
		Unspecified "ARBs"	Candesartan cilexetil	Eprosartan	Irbesartan	Losartan	Olmesartan medoxomil	Telmisartan	Valsartan	Aliskiren	Totals
ACEIs	Unspecified "ACEIs"	21 (24)	0	0	2 (2)	1 (1)	0	0	0	0	24 (27)
	Benazepril	0	0	0	0	0	0	0	1 (1)	0	1 (1)
	Captopril	0	0	0	0	2 (2)	0	0	0	0	2 (2)
	Enalapril	0	4 (4)	2 (6)	4 (4)	14 (15)	0	5 (5)	2 (2)	0	31 (36)
	Fosinopril	0	0	0	2 (2)	1 (1)	0	0	0	0	3 (3)
	Lisinopril	0	6 (6)	0	0	1 (1)	0	3 (3)	5 (5)	0	15 (15)
	Moexipril	0	0	0	0	0	0	0	0	0	0
	Perindopril	0	1 (1)	0	0	3 (3)	0	3 (3)	0	0	7 (7)
	Quinapril	0	0	0	2 (2)	3 (3)	0	0	0	0	5 (5)
	Ramipril	0	0	0	0	2 (2)	1 (1)	5 (5)	3 (3)	2 (3)	13 (14)
	Trandolapril	0	0	0	0	1 (1)	0	0	0	0	1 (1)
DRI	Aliskiren	0	0	0	0	1 (1)	0	0	0	-	1 (1)
	Totals	21 (24)	11 (11)	2 (6)	10 (10)	29 (30)	0	16 (16)	11 (11)	2 (3)	-

*Totals exceed 100 studies/110 publications because some trials reported on more than one ACE-inhibitor versus ARB treatment comparison.

As Table 4 illustrates, enalapril was by far the most frequently studied ACEI (31 studies) and losartan the most frequently studied ARB (29 studies), followed by telmisartan (16 studies). The most commonly studied treatment comparison was the generic "ACEIs" versus "ARBs" (21 studies), followed by enalapril versus losartan (14 studies). Other treatment comparisons were fairly sparsely represented.

In terms of quality, 54 studies were rated as fair, 30 as poor, and 16 as good. The distribution of studies by followup time is given in Table 5.

Table 5. Distribution of studies by followup time

Treatment duration/followup time	Report studies
12 weeks	23
14–16 weeks/3–4 months	15
22 weeks	1
24–26 weeks/6 months	22
30 weeks	1
36 weeks	2
10–11 months	2
48 weeks	4
1 year	16
15 months	1
1.8 years	1
720 days	1
2 years	1
33 months	1
3 years	4
39 months	1
4 years	2
5 years	1
~ 70 months	1

There was no obvious correlation between study quality and length of followup. The 16 good-quality studies varied in length from 12 weeks (3 studies), 13 to 36 weeks (7 studies), 1 year (4 studies), to 2 years (2 studies).

Key Question 1. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes?

Key Points

- There was no clear difference in blood pressure lowering efficacy between ACEIs and ARBs. Data concerning direct renin inhibitors were limited.

- Few deaths or major cardiovascular events occurred in the identified studies comparing ACEIs, ARBs, and direct renin inhibitors; this significantly limited any assessment of a differential effect of these drug classes on these events.
- No significant difference was observed between ACEIs and ARBs in terms of their impact on quality of life. No evidence was available regarding the impact of direct renin inhibitors on quality of life.
- There was no statistically evident difference in rate of treatment success based on use of a single antihypertensive medication for ARBs compared to ACEIs. No evidence regarding the effect of direct renin inhibitors on this outcome was identified.
- Available evidence suggests that ACEIs and ARBs have a similar lack of impact on lipid levels for individuals with essential hypertension. No evidence regarding the effect of direct renin inhibitors on these outcomes was available.
- Available evidence suggests that ACEIs and ARBs have a similar lack of impact on glucose levels or HbA1c for individuals with essential hypertension. No evidence regarding the effect of direct renin inhibitors on these outcomes was available.
- Evidence does not demonstrate a difference between ACEIs, ARBs, and direct renin inhibitors with regard to their effect on left ventricular (LV) mass or function for individuals with essential hypertension.
- There are no consistently demonstrated differential effects related to renal function as measured by creatinine or glomerular filtration rate (GFR) with use of ACEIs, ARBs, or direct renin inhibitors. There appears to be a small difference in change in renal function favoring ACEIs over ARBs, but the clinical significance of these small effects is uncertain.
- There is a consistent finding of no differential effect related to reduction of urinary protein or albumin excretion among patients with essential hypertension with use of ACEIs, ARBs, or direct renin inhibitors.

Effect on Blood Pressure

Comparisons of ACEIs Versus ARBs

Seventy-seven studies described in 83 separate publications met our inclusion criteria and reported a blood pressure outcome. Of these, 12 (16 percent) were of good methodological quality,[23-34] 42 (55 percent; 47 papers) were of fair quality,[35-78] and 23 (30 percent) were of poor quality.[79-102] There were 5 nonrandomized controlled clinical trials,[80,83,84,89,96] 1 retrospective cohort study,[49] and 1 case-control study;[99] the remaining 70 studies were RCTs. Sample sizes for individual studies ranged from 24 patients to 3,813 patients, and a total of 26,170 patients received an ACEI or an ARB. Study durations ranged from 12 weeks to 5 years, with a median of 24 weeks.

The mean age of study participants ranged from 33 years old to 73 years old, with a median of 55.4 years old. The proportion of female patients included ranged from 19 percent to 100 percent, with a median of 48 percent. Only 33 studies (43 percent; 39 papers) reported the racial demographics of the study participants.[25,26,29,30,32-40,43,48,52-56,58,61,63,64,69,71,75-77,80,91,92,97,103-108] Of these 33 studies, only 12 (36 percent; 17 papers) enrolled a minimum of 10 percent of ethnic minority participants.[29,36,38,39,43,48,52,54-56,61,63,76,97,103,104,106]

Seven studies (9 percent) were conducted entirely within the United States or Canada,[29,38,52,53,63,76,106] with the remainder carried out in other countries. The funding source was

reported in 44 studies (57 percent; 49 papers),[25-33,36-40,42,43,48-50,52-62,65-67,69-71,74,78-80,83,92-95,97-99,109] with the majority of these (29 studies) funded by the manufacturer of one of the study medications.

The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the beginning of each study ranged from 127 to 199 mm Hg and 67 to 119 mm Hg, respectively, with a mean starting blood pressure of 156/97 mm Hg. There was significant heterogeneity in the study protocols and data reporting. Fewer than half of the studies (30/77; 39 percent; 31 papers) did not allow additional hypertension medications during the study;[23,25,27,35,38,40,41,44,45,47,56-59,64-66,69,72,74,75,77,80,83,85,87,91,92,102,106,108] 29 studies (38 percent; 33 papers) allowed additional medications according to a specified protocol;[26,28,29,31-34,36,39,43,48,50-55,61,63,67,68,70,71,73,76,78,82,86,88,98-100,109] 6 studies (8 percent; 7 papers) allowed additional medications at the discretion of the treating physician;[30,37,49,60,62,94,95] and 12 studies (16 percent) did not report concomitant hypertension therapy.[24,42,46,79,81,84,89,90,93,96,97,101] The reported blood pressure endpoints varied as well, with 51 studies (66 percent; 53 papers) reporting the difference in final post-treatment blood pressure;[25,26,29,31-34,40-42,44-47,50,53,56,58,61-68,70,71,74,75,77-83,86-88,90-99,101,102,106] 35 studies (45 percent; 40 papers) reporting the mean change in blood pressure in each study arm;[23,24,26-30,35-40,43-46,48,49,51,52,54-58,60,61,63,64,69,73,75,76,84,85,91,100,106,108] and 4 studies (5 percent) not providing quantitative data for the blood pressure outcome or reporting only the proportion of patients achieving a target blood pressure.[59,72,89,109]

For the overall comparison of blood pressure lowering between ACEIs and ARBs, 57 studies reported no difference (74 percent; 62 papers),[23,24,26,28,30-34,36-44,46,48,50-55,58-63,65-67,70-74,76-82,86-90,92-101,109] 2 studies favored ACEIs (3 percent; 3 papers),[29,64,75] 11 studies favored ARBs (14 percent),[25,27,35,45,47,56,57,69,91,106,108] and 6 studies (8 percent) did not report the comparison between the two agents.[49,68,83-85,102] We did not detect any specific ACEI or ARB that performed better or worse than other medications in its class.

Blood pressure outcomes were confounded by protocols calling for dose escalation or adding additional blood pressure-lowering drugs; such protocols differed substantially between studies, making the blood pressure outcomes difficult to interpret. Overall, there was no clear difference in the blood pressure lowering efficacy between the two classes of agents, no matter what criteria were used for study inclusion. Because of the heterogeneity in study protocols, quantitative meta-analysis was not performed. However, despite some differences in methods for measuring successful control of blood pressure on a single agent, this outcome seemed to represent a reasonable comparison that was not confounded by substantial differences between studies. Therefore, quantitative meta-analysis was performed for this outcome.

Caveats and concerns include the fact that there was significant heterogeneity in the medication protocols and the use of concomitant hypertension therapy. Many of the studies reported limited data on patient characteristics, and black patients appeared to be significantly underrepresented overall. Very few of the studies were considered to be of good methodological quality. In addition, the majority of the studies reporting a funding source were sponsored by the manufacturer of the ARB.

Comparisons of Direct Renin Inhibitors Versus ACEIs or ARBs

We identified three studies (four publications) comparing the direct renin inhibitor aliskiren with either an ACEI or ARB.[103-105,107] All three studies were good-quality RCTs. Two compared the ACEI ramipril at a maximum dose of 10 mg to aliskiren at a maximum dose of 300 mg and used a similar protocol that allowed additional medications to be added if the blood pressure was

above target at 12 weeks. In both studies, aliskiren produced a greater reduction in blood pressure compared to ramipril at 12 weeks, with between-group blood pressure (SBP/DBP) differences of -2.7/-1.6[103,104] and -2.3/-1.5 mmHg.[105] The third study compared aliskiren to the ARB losartan and reported no significant differences in blood pressure lowering or in use of single antihypertensive agent.[107]

Effect on Mortality and Major Cardiovascular Events

The literature review identified 26 publications[25,26,28,30,32,36,37,39,43,48,52,53,55,74,88,98,101,103-105,107,108,110-113] describing 21 separate studies that reported patient mortality, myocardial infarction (MI), or clinical stroke as outcomes. Seventeen studies (22 publications) were RCTs.[25,26,28,30,32,36,37,39,43,48,52,53,55,74,88,98,101,103-105,107,108] The 21 studies reported on 40,749 patients (38,589 of whom received an ACEI, an ARB, or a DRI) and ranged in duration from 12 weeks to 5 years; most reported blood pressure measurements as primary endpoints. The treatment comparisons evaluated were (one study per comparison, unless otherwise noted):

- "ACEIs" versus "ARBs" (3 studies);[110,112,113]
- Candesartan versus lisinopril;[32]
- Eprosartan versus enalapril (2 studies, 6 publications);[30,36,39,43,48,55]
- Losartan versus enalapril (2 studies);[53,74]
- Losartan versus fosinopril;[88]
- Losartan versus ramipril;[98]
- Losartan versus quinapirl;[52]
- Telmisartan versus ramipril;[108]
- Telmisartan versus enalapril (2 studies);[37,101]
- Valsartan versus lisinopril (3 studies);[26,28,111]
- Valsartan versus enalapril;[25]
- Aliskiren versus ramipril (2 studies, 3 publications);[103-105] and
- Aliskiren versus losartan.[107]

The studies were of good (n = 8), fair (n = 9), and poor (n = 4) quality. Notably, the majority of studies in this review—including those reporting mortality and major cardiovascular events—excluded patients with significant cardiovascular disease and often other comorbid conditions.

The studies evaluated shed little light on the issue of relative rates of mortality, MI, or stroke with ACEIs versus ARBs versus direct renin inhibitors. In 21 studies involving 40,749 patients, 38 patients died. The study by Barnett et al.[37] provided the most and the longest-term data on cardiovascular events. This study evaluated telmisartan versus enalapril in 250 patients with type 2 diabetes and early nephropathy over a 5-year treatment period. In this higher risk population, cardiovascular events occurred at a similar rate in both treatment groups: there were six strokes in each group; nine nonfatal MIs in the telmisartan group and six in the enalapril group; and nine patients with heart failure in the telmisartan group and six in the enalapril group. This study also reported 12 deaths, 6 in the telmisartan group (3 due to stroke, MI, and heart failure), and 6 in the enalapril group (2 due to MI).

Among shorter-term trials, the study by Ruilope et al.,[30] evaluating eprosartan versus enalapril over 12 weeks, reported one death in each group, a 95-year-old patient with cancer and an 80-year-old patient with heart failure. Shibaskaki et al.[74] evaluated losartan versus enalapril versus amlodipine over 6 months and reported one death due to pulmonary hemorrhage, and one patient with MI; the treatment group to which the patient belonged was not specified for either

event. The paper by Elliott et al.[43] is the primary report of a trial of eprosartan versus enalapril over 26 weeks. A substudy from this trial published by Gavras et al.[48] reported that one patient assigned to the eprosartan group had an anteroseptal MI and died. Williams et al.[108] evaluated telmisartan versus ramipril over 14 weeks and reported that one patient in the ramipril group had a stroke. An RCT by Andersen et al.[103,104] comparing aliskiren to ramipril noted one death due to mesenteric thrombosis in the ramipril group. An RCT comparing valsartan, lisinopril, or their combination noted one death in the lisinopril group and one in the combination group.[28] Delea et al.[111] performed a retrospective cohort study using administrative data and found cardiovascular event rates to be similar between patients taking valsartan versus lisinopril after adjusting for possible confounding characteristics. Finally, Spinar et al.[98] described two studies in one publication: one a single-arm trial of losartan (n = 4,016), and the other an RCT of losartan versus ramipril (n = 3,813). The single-arm study reported a mortality rate of 0.1 percent over 1 year, with MI occurring in 0.2 percent of participants and stroke in 0.3 percent of participants. In the RCT, the rates of both mortality and MI were 0.2 percent, and the stroke rate was 0.4 to 0.5 percent in both treatment groups. In none of these trials did investigators attribute any of the events observed directly to therapy.

Effect on Quality of Life

Four studies described in eight separate papers reported data on quality of life.[36,39,41,43,48,51,55,57] All four were RCTs comparing ACEIs versus ARBs, and all were rated as fair in methodological quality. However, with regard to assessing quality of life, two of the four could be considered poor, as they did not present quantitative data.[51,57]

Sample sizes for the individual studies ranged from 42 to 528 patients, with a total of 1,142 patients. Study durations ranged from 12 weeks to 3 years, with a mean of 55 weeks (median 26 weeks). Only one of the four studies reported the racial demographics of the study participants;[43] in that study, 14 percent of participants were members of ethnic minorities. Studies utilized a variety of quality-of-life scales: two administered the Psychological General Well Being with its six subscales;[43,57] two administered the Subjective Symptoms Assessment profile;[41,43] one study employed the McMaster Overall Treatment Evaluation Questionnaire;[57] and one used the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36).[51] Only two studies presented any quantitative data to support their conclusions of no difference in the impact of ACEIs or ARBs on quality of life.[41,43]

None of the studies found any difference between ACEIs and ARBs in their impact on the quality of life of study participants; indeed, no study demonstrated an impact on quality of life for subjects treated with ACEIs or ARBs. Finally, none of the studies comparing direct renin inhibitors with ACEIs or ARBs reported data on quality of life.

Effect on Rate of Use of a Single Antihypertensive Agent

We identified 26 studies that reported the outcome of successful monotherapy for ACEIs versus ARBs.[26-30,34,36,45,49-54,60,63,68,70,71,76,77,82,86,88,99,109,114] The definition of "successful" monotherapy differed between studies and included SBP or DBP below a specified cutoff, or monotherapy defined by a lack of additional antihypertensive medication at the end of the study. Six studies were determined to be of good quality, 17 were fair in quality, and 4 were poor. There were 24 RCTs, 2 retrospective cohorts, and 1 case-control study. Sample sizes ranged from 30 patients to 13,303 patients. Study durations ranged from 12 weeks to 3.3 years, with a

median of 26 weeks. The rates of successful monotherapy ranged between 6 percent and 93.3 percent (median 55 percent).

We performed a meta-analysis of data from the 26 studies. Individual study estimates for the differences between ACEIs and ARBs in the proportion of patients achieving successful blood pressure control on a single agent showed no statistical heterogeneity (Q = 36.6; df = 25; p = 0.063). A summary estimate of the odds ratio for the proportion of patients with successful blood pressure control on a single agent with ARBs compared to ACEIs was 1.128 (95% CI 1.002 to 1.270; p = 0.047; random-effects model).

Table 6 summarizes the studies and their estimated odds ratios. The odds ratio represents the odds of successful blood pressure control for ARB patients divided by the odds of successful blood pressure control for ACEI patients.

Table 6. Estimated odds ratios for successful blood pressure control on monotherapy (ARBs vs. ACEIs)

Study	Odds ratio	Ln(OR)	Standard error	Study type
Verdecchia et al., 2000[99]	1.2750	0.2429	0.4940	OBS
Hasford et al., 2002[49]	1.5088	0.4113	0.1328	OBS
Mazzaglia et al., 2005[114]	1.1083	0.1028	0.0711	OBS
Townsend et al., 1995[76]	0.7873	-0.2391	0.2448	RCT
Ruff et al., 1996[29]	0.3351	-1.0933	0.8076	RCT
Larochelle et al., 1997[54]	1.4250	0.3542	0.6063	RCT
Argenziano et al., 1999[36]	1.0000	0.0000	0.1881	RCT
Karlberg et al., 1999[51]	1.0316	0.0311	0.2494	RCT
Neutel et al., 1999[63]	0.8413	-0.1728	0.1769	RCT
Lacourciere et al., 2000[53]	0.4375	-0.8267	0.4027	RCT
Mogensen et al., 2000[60]	1.7609	0.5658	0.4233	RCT
Ruilope et al., 2001[30]	0.7382	-0.3036	0.4131	RCT
Cuspidi et al., 2002[109]	1.0048	0.0048	0.2597	RCT
Kavgaci et al., 2002[88]	0.7959	-0.2283	0.8342	RCT
Eguchi et al., 2003[82]	0.8750	-0.1335	0.5804	RCT
Ghiadoni et al., 2003[86]	1.2778	0.2451	0.6329	RCT
Fogari et al., 2004[45]	1.3846	0.3254	0.3301	RCT
Malacco et al., 2004[26]	1.0400	0.0392	0.1410	RCT
Robles et al., 2004[68]	0.7273	-0.3185	0.8006	RCT
Saito et al., 2004[71]	1.5742	0.4537	0.2199	RCT
Rosei et al., 2005[70]	0.8306	-0.1857	0.3622	RCT
Uchiyama-Tanaka et al., 2005[77]	1.1053	0.1001	0.7353	RCT
Tedesco et al., 2006[34]	0.9240	-0.0791	0.3036	RCT
Hosohata et al., 2007[50]	1.9360	0.6606	0.1920	RCT
Menne et al., 2008[28]	0.9974	-0.0026	0.4838	RCT
Malacco et al, 2010[27]	1.4069	0.3414	0.1216	RCT

Ln(OR) = natural log of odds ratio; OBS = observational study; RCT = randomized controlled trial

We summarized all studies together and also analyzed RCTs and observational studies separately. Results for both fixed-effect and random-effects analyses are given in Table 7. The analyses include measures of homogeneity (Q-statistic). Results of an analysis of the potential for publication bias are provided in Appendix H.

Table 7. Meta-analyses of successful blood pressure control on monotherapy by subgroup for ARBs versus ACEIs

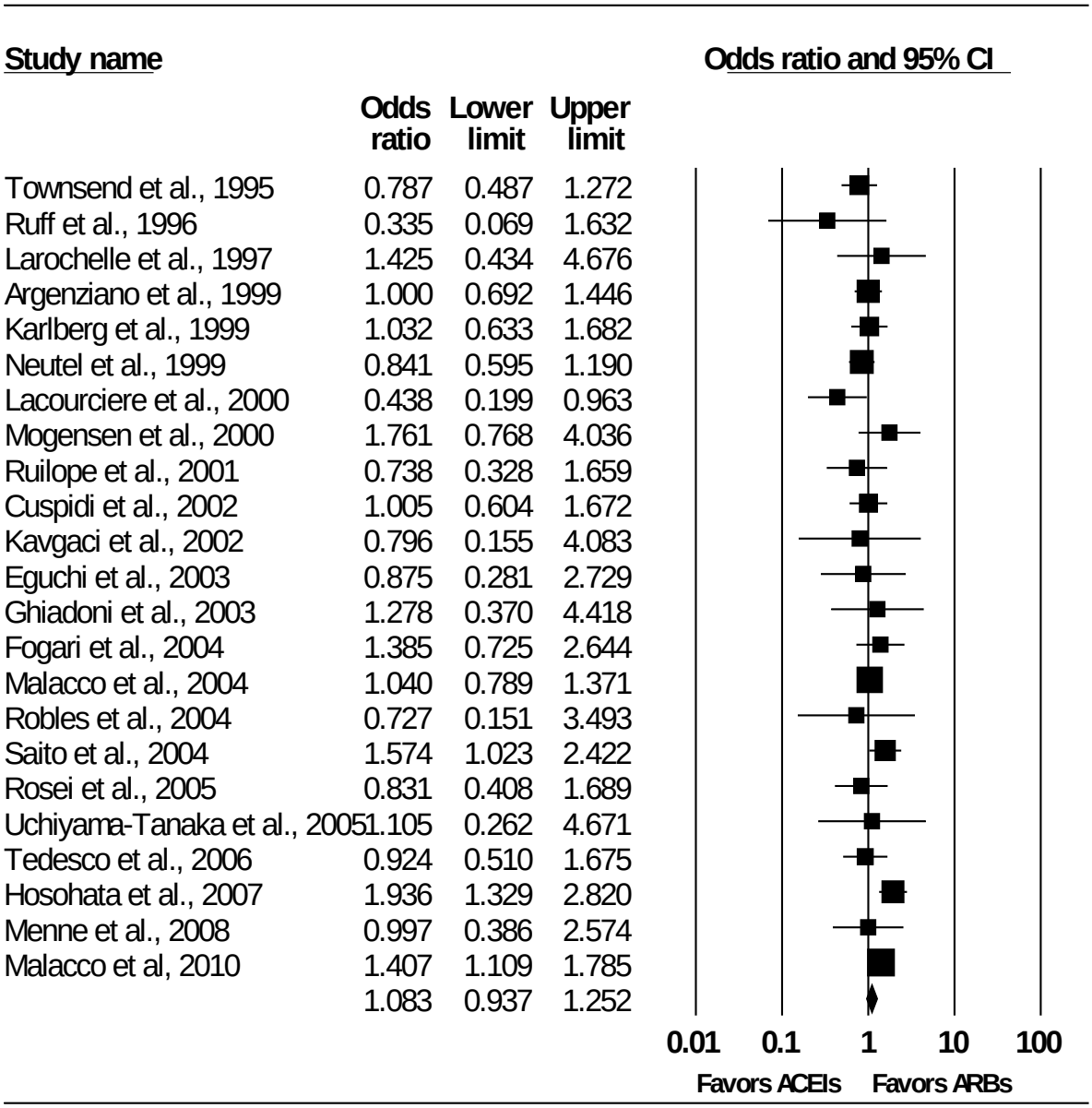
Model	Analysis subgroup	No. of studies	OR estimate	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	26	1.151	1.062	1.247	3.437	0.001	36.566	25	0.063
Random	All	26	1.128	1.002	1.270	1.986	0.047			
Fixed	Observ	3	1.188	1.052	1.342	2.776	0.006	4.214	2	0.122
Random	Observ	3	1.258	0.984	1.610	1.829	0.067			
Fixed	RCTs	23	1.123	1.010	1.250	2.138	0.033	31.887	22	0.079
Random	RCTs	23	1.083	0.937	1.252	1.076	0.282			

CI = confidence interval; df = degrees of freedom; Observ = observational studies; OR = odds ratio; RCTs = randomized controlled trials

Because the definition of successful control of blood pressure with a single agent requires that a patient remain on the originally prescribed drug and receive no additional antihypertensive agent, "successful monotherapy" reflects both the efficacy of the medication and tolerability and adherence to the prescribed therapy. When we examined our results separately for observational and experimental studies, the trend favoring ARBs for this outcome appeared to be driven primarily by differences in tolerability and adherence, since the benefit of ARBs appeared different in retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients.

The results for the random-effects analysis of RCTs alone are shown in Figure 3.

Figure 3. Random-effects analysis of RCTs for successful blood pressure control on monotherapy (ARBs vs. ACEIs)

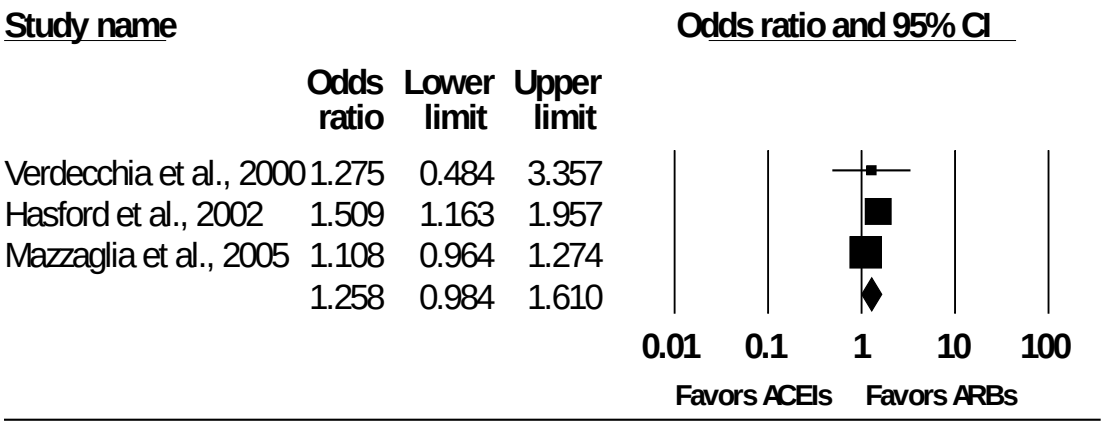


The results for this outcome are best summarized by the random-effects analysis of the RCTs shown in Figure 3. This analysis gave an estimated odds ratio of 1.083 (95 percent CI 0.937 to 1.252), suggesting that the odds of successful blood pressure control is only 8 percent larger with an ARB alone than with an ACEI alone, and this amount is not statistically significant.

These odds ratios need to be compared against the overall successful blood pressure control rate for monotherapy with ACEIs. If we pool all of the RCTs, we get a rate of about 54.7 percent.

The results for the random-effects analysis of the observational studies alone are shown in Figure 4.

Figure 4. Random-effects analysis of observational studies for successful blood pressure control on monotherapy (ARBs vs. ACEIs)



This analysis gave an estimated odds ratio of 1.258 (95% CI 0.984 to 1.610), suggesting that the odds of successful blood pressure control is 26 percent larger with an ARB alone than with an ACEI alone, and this amount is marginally statistically significant (p = 0.0673).

These odds ratios need to be compared against the overall successful blood pressure control rate for monotherapy with ACEIs. If we pool all of the observational studies, we get a rate of about 24.9 percent. While the magnitude of relative increase in successful monotherapy with ARBs represents a clinically important difference, this result should be interpreted with caution. The lack of concordance between pooled results in RCTs and observational studies suggests selection bias and residual confounding as potential explanations for this observed difference, rather than the inherent efficacy of the medication.

We did not identify any studies comparing a direct renin inhibitor with an ACEI or an ARB for this outcome.

Effect on Serum Lipid Levels

Twenty studies described in 25 papers met our inclusion criteria and evaluated serum lipid changes. Seventeen of the 20 studies were RCTs,[23,25,32,34,43,44,46,53,62,70,73,75,77,86,88,101,102] 1 was a nonrandomized three-arm parallel-group clinical trial,[96] and 1 was an observational case-control study.[99] One publication[98] reported results from two studies: an RCT and a single-arm clinical trial of an ARB with an ACEI as a preintervention comparison (participants were switched from an ACEI to losartan). The ACEI-versus-ARB treatment comparisons were unique in 14 studies; 4 studies compared losartan versus enalapril,[34,53,75,99] 2 compared telmisartan versus perindopril,[62,86] and 2 compared telmisartan versus enalapril.[37,101] Study periods ranged from 3 to 24 months, all of which were sufficiently long to detect measurable changes in the lipid profile.

Most of the 20 studies were fair in quality, and none addressed the use of lipid-lowering agents during the study period. The four studies rated as good in quality[23,25,32,34] took place in Europe and were moderate to large in sample size (range 70 to 520); one study was of short duration (16 weeks);[25] two were of medium duration (12 months);[23,32] and one was long (24 months).[34] Two of the good-quality studies targeted patients with diabetes.[23,32]

The majority of the available head-to-head evidence suggests that ACEIs and ARBs have a similar lack of impact on lipid parameters. Twelve studies found no within-group change during

treatment in total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and/or triglyceride (TG) levels during the study period. Four studies found statistically significant within-group treatment effects but did not report between-group comparisons (Table 8): TC and TG decreased with fosinopril, while TG decreased with losartan in one study;[88] TC decreased with losartan in another study;[34] TC decreased with losartan and enalapril, LDL decreased with losartan, and TG decreased with enalapril in a third study;[53] and TC, TG, and LDL decreased, while HDL increased, with both ramipril and valsartan in the fourth study.[102]

Twelve studies directly compared outcomes between ACEI and ARB groups.[23,25,44,46,62,70,73,75,96,98,99,101] Of these 12, only two found different effects between the medications compared (Table 8). One study reported a decrease in LDL that was statistically greater in the ACEI group (perindopril -14 percent vs. candesartan -4 percent).[23] Another study found a statistically greater decrease in triglyceride (telmisartan -28 percent vs. enalapril -6 percent, $p < 0.01$) and greater increase in HDL (telmisartan +18 percent vs. enalapril -3 percent, $p < 0.05$) for telmisartan compared with enalapril.[101] Thus, for the two studies in which a difference between groups was found, the difference was discrepant (i.e., results favored ACEI in one study and favored ARB in the other). Of these two studies, only one was rated as good in quality.[23]

Table 8. Studies reporting significant changes in lipid profiles with ACEIs and/or ARBs

Study	N	Population	Quality	Comparators	ΔTC	ΔLDL	ΔHDL	ΔTG
Lacourciere et al., 2000[53]	103	- Mean age 58 - 96% white - Canada - Diabetes	Fair	Losartan vs. enalapril	-2.1%* vs. -4.2%*	-6.5%* vs. NR	NR	NR vs. -11.3%*
Derosa et al., 2003[23]	96	- Mean age 54 - Europe - Diabetes	Good	Candesartan vs. perindopril	-1 mg/dL vs. -12 mg/dL*†	-4 mg/dL vs. -14 mg/dL†	+2 mg/dL vs. -2 mg/DL	+2 mg/dL vs. -22 mg/dL
Kavgaci et al., 2002[88]	33	- Mean age 53 - 100% white - Turkey - Diabetes	Poor	Losartan vs. fosinopril	+0.01% vs. -0.1%*	NR	NR	-0.23%* vs. -0.21%*
Tedesco et al., 2006[34]	520	- Mean age 54 - 100% white - Italy - No diabetes	Good	Losartan vs. enalapril	-10 mg/dL* vs. +1 mg/dL	NR	NR	NR
Yilmaz et al., 2007[102]	96	- Mean age 48 - Turkey - Metabolic syndrome	Poor	Ramipril vs. valsartan	14.3 to 12.0 mmol/L* vs. 14.9 to 12.6 mmol/L*	7.3 to 5.5 mmol/L* vs. 7.7 to 6.1 mmol/L*	2.0 to 2.4 mmol/L* vs. 1.9 to 2.3 mmol/L*	8.8 to 7.6 mmol/L* vs. 11.0 to 8.9 mmol/L*
Xu et al., 2007[101]	96	- Mean age 51 - China - Abnormal serum lipids	Poor	Telmisartan vs. enalapril	6.1 to 5.8 mmol/L vs. 6.1 to 5.9 mmol/L	3.1 to 2.3 mmol/L vs. 3.1 to 3.0 mmol/L	1.5 to 1.7 mmol/L† vs. 1.4 to 1.4 mmol/L	2.8 to 2.0 mmol/L† vs. 2.8 to 2.6 mmol/L

*Statistically significant within-treatment change (baseline to followup)
†Statistically significant comparison between treatments
HDL = low-density lipoprotein; LDL = low-density lipoprotein; N = number of subjects; NR=not reported; TC = total cholesterol; TG = triglyceride

Effect on Markers of Carbohydrate Metabolism/Diabetes Control

Twenty-three studies described in 28 papers met our inclusion criteria and measured glucose or HbA1c. All but four[80,96,99,110] were RCTs. Overall, only 3 studies were rated as good in quality;[23,25,32] the remainder were rated as either fair (11 studies[43,44,46,53,60,62,72,73,75,77,110]) or poor (9 studies[80,86,88,96,98,99,101,102,113]). The ACEI-versus-ARB comparisons tested were unique in 14 studies; of the remaining 9 studies, enalapril and losartan were compared in 5,[53,75,80,96,99] candesartan and lisinopril in 2,[32,60] and perindopril and telmisartan in 2.[62,86]

It is relevant that none of the 23 studies measuring glucose or HbA1c changes addressed hypoglycemic therapy during the study period, and only 8 were specifically performed in diabetic populations.[23,32,44,53,60,73,88,113] Of the other 15 studies, 4 permitted controlled diabetic patients but did not describe their proportion in the cohort;[43,72,75,99] 5 permitted diabetic subjects;[62,77,96,98,110] and 6 specifically excluded individuals with diabetes.[25,46,80,86,101,102]

The majority of the available head-to-head evidence suggests that ACEIs and ARBs have a similar lack of impact on glucose levels or HbA1c. Twelve studies directly compared outcomes between the ACEI and ARB groups.[23,25,44,46,62,72,75,80,99,101,110,113] One study reported a small decrease in glucose after 12 months that was statistically greater in the ACEI group (perindopril -15 ± 4 mg/dL, candesartan -8 ± 2 mg/dL),[23] and one reported a significant increase in HbA1c (+ 0.25 percent enalapril vs. + 0.6 percent losartan) but did not directly compare the two groups.[53] One study reported significantly lower 2-hour blood glucose levels at 6 months in the telmisartan group (5.48 mmol/L ± 1.46) compared with the enalapril group (6.70 mmol/L ± 1.41, $p < 0.05$).[101] Of these three studies, only one[23] was rated as good in quality. The other nine studies that analyzed differences in outcomes between the two groups did not find a difference. Sixteen studies compared baseline to followup glucose levels or HbA1c and found no change for either the ACEI or ARB groups.

Effect on Measures of LV Mass or Function

Thirteen studies presented results on LV mass or function assessed either by LV mass index (LVMI; 7 studies),[31,33,34,41,80,99,107] LV ejection fraction (LVEF; 2 studies),[81,93] both (3 studies),[74,92,109] or LV posterior wall thickness.[87] Table 9 summarizes relevant characteristics of all 13 studies. Six of these studies had fewer than 50 patients,[33,41,74,80,87,93] 2 had between 50 and 100 patients,[31,99] and 5 had 100 or more patients.[34,81,92,107,109] All but two studies[80,99] were RCTs. Only two studies had relatively long-term followup (≥ 3 years);[41,99] however, the majority of studies had between 6 and 12 months of followup,31,33,74,80,81,87,92,107,109 while one study had only 3 months of followup.[93] Because duration of therapy may significantly impact the ability to observe changes in LV mass or function, negative results must be interpreted with caution in studies with short-term followup.

Table 9. Characteristics of studies reporting LV mass/function outcomes

Study	Agents studied	Population	Design and size*	Duration	Quality	Outcome	Result
Cuspidi et al., 2002[109]	Candesartan vs. enalapril	LVH (29–32%)	RCT N = 196 (145)	48 wk	Fair	LVMI & LVEF	↓LVMI both, no difference between agents, no change in LVEF
Spoelstra-de Man et al., 2006[33]	Candesartan vs. lisinopril	DM and HTN (? %LVH)	RCT N = 46	12 mo	Good	LVMI	↓LVMI both, but ARB not compared to ACEI
Schieffer et al., 2004[93]	Irbesartan vs. enalapril	CAD (? %LVH)	RCT N = 60 (48)	3 mo	Poor	LVEF	No difference No detailed data by treatment group
Guntekin et al., 2008[87]	Irbesartan vs. quinapril	New HTN (? %LVH)	RCT N = 65 (38)	12 mo	Poor	LV posterior wall thickness	↓LV posterior wall thickness both, no difference reported between agents
Avanza et al., 2000[80]	Losartan vs. enalapril	LVH (100%)	Non-rand controlled clinical trial N = 30	10 mo	Poor	LVMI	↓LVMI both, no difference between agents, combo ACEI/ARB best
De Rosa et al., 2002[41]	Losartan vs. enalapril	LVH (44–53%)	RCT N = 50 (42)	3 yr	Fair	LVMI	Non-statistical ↓LVMI both, no difference between agents
Shibasaki et al., 2002[74]	Losartan vs. enalapril	ESRD with LVH (100%)	RCT N = 20	6 mo	Fair	LVMI & LVEF	↓LVMI both, ARB better than ACEI, no change in LVEF
Tedesco et al., 2006[34]	Losartan vs. enalapril	HTN (30–33% LVH)	RCT N = 259 (185)	2 yr	Good	LVMI	↓LVMI both, ARB more than ACEI, but ARB higher baseline
Verdecchia et al., 2000[99]	Losartan vs. enalapril	LVH (23–24%)	Case-control N = 88	3.3 yr	Poor	LVMI	↓LVMI both, no difference between agents
Rajzer et al., 2003[92]	Losartan vs. quinapril	HTN (? %LVH)	RCT N = 118	6 mo	Poor	LVMI & LVEF	No change in LVMI or LVEF in either group No detailed data by treatment group
Scaglione et al., 2007[31]	Losartan vs. ramipril	HTN (53% LVH)	RCT N = 57	24 wks	Good	LVMI	↓LVMI both, no difference between agents
Celik et al., 2005[81]	Telmisartan vs. ramipril	HTN (? %LVH)	RCT N = 100	6 mo	Poor	LVEF	No change in LVEF in either group
Solomon et al., 2009[107]	Aliskiren vs. losartan	HTN (100% LVH)	RCT N = 465 (400)	34 wks	Good	LVMI	↓LVMI both, no difference between groups (aliskiren, ARB, combination)

* Size of study includes total enrolled in ACEI, ARB, direct renin inhibitor, or combination arms, with relevant followup population (if different) in parentheses.

CAD = coronary artery disease; ESRD = end-stage renal disease; HTN = hypertension; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; mo = months; RCT = randomized controlled trial; wk = weeks; yr = years

Evidence provided by the 13 studies identified did not demonstrate a difference between ACEIs and ARBs with regard to LV mass or function for individuals with essential hypertension. Ten studies reported detailed data by treatment groups,[31,33,34,41,74,80,81,99,107,109] while one reported summary data,[92] and two described changes without presenting any data.[87,93] In general, the

quality ratings of these studies describing changes in LV mass or function was poor,[80,81,87,92,93,99] although some of the more recent ones were rated as being good-quality studies.[31,33,34,107] Various ARBs and ACEIs were studied, including seven studies with losartan[31,34,41,74,80,92,99] and seven studies with enalapril.[34,41,74,80,93,99,109] Only one study evaluated the newer direct renin inhibitor, aliskiren.[107] Among the nine studies that presented detailed data on outcomes, six assessed LVMI,[31,34,41,80,99,107] one assessed LVEF,[81] and two assessed both LVMI and LVEF.[74,109]

The best and largest (n = 259) comparative study (an RCT) assessed LVMI at baseline and after 24 months of followup.[34] The authors reported similar decreases in mean LVMI in both groups in per-protocol analyses (12.3 percent on losartan versus 7.5 percent on enalapril). The trial with the longest followup (3 years; RCT) also reported similar reductions in mean LVMI in both groups; however, these changes did not reach statistical significance.[41] Two nonrandomized studies reported similar decreases in LVMI,[80,99] with one[80] demonstrating additional benefit in LVMI reduction with combination ACEI and ARB therapy. Only one study demonstrated a difference between groups for reduction in LVMI,[74] with lower reduction among those treated with losartan versus enalapril (24.7 ± 3.2 percent vs. 11.2 ± 4.1 percent; p = 0.026). However, definitive conclusions from this study are limited because it was conducted in patients with end-stage renal disease, included only 10 patients per treatment group, and had only moderate duration of followup (6 months). Finally, among the studies that reported results for LVEF, none demonstrated any differential effects between the ACEI and ARB groups.

Despite differences in sample size, study design, length of followup, study quality, therapeutic agents, and outcome measure, most of the studies demonstrated either similar improvements in LV mass or function between the ACEI and ARB groups[31,33,34,74,80,87,99,109] or no change.[41,92] Similar improvements in LV mass were also observed in the direct renin inhibitor study.[107] Reductions in LVMI appear to have occurred particularly among patients with established LV hypertrophy.[41,74,80,109] No changes in LVEF were observed in any of the studies. In sum, this body of poor- to fair-quality evidence does not demonstrate any differential effects in the ability of ACEIs, ARBs, and direct renin inhibitors to improve or stabilize LVMI in patients with essential hypertension.

Effect on Serum Creatinine/GFR and Proteinuria

Overview

Review of the literature on the relative effects of ACEIs, ARBs, and direct renin inhibitors on changes in intermediate renal outcomes identified 31 studies described in 38 publications. One of these studies was conducted in patients with end-stage renal disease who had been on maintenance hemodialysis for at least 1 month.[74] This study is not considered further here, as no changes would be expected in the outcome assessed (serum creatinine) in the population studied. Of the remaining 30 studies, 12 assessed either serum creatinine or GFR,[25,41,43,44,59,69,77,80,94,98,99,105] 6 assessed proteinuria;[23,28,32,60,103,115] and 12 assessed both.[37,42,53,62,70,73,75,78,88,90,110,113] Most studies included fewer than 100 patients; however, 10 had approximately 200 patients or more.[37,43,59,60,69,73,75,98,104,105] All but five[80,99,110,113,115] were RCTs. One study[37] followed patients for 5 years, and approximately half of the studies had at least 1 year of followup; however, four studies followed patients for less than 4 months.[44,59,75,94]

Results for Creatinine-Related Outcomes

The 24 studies that described changes in creatinine or GFR did not consistently demonstrate differential effects related to renal function with use of ACEIs versus ARBs. Seventeen of these studies reported detailed data by treatment groups,[25,37,41,42,44,59,62,73,77,78,80,88,94,99,105,110,113] while three reported summary data,[53,75,98] and five described the changes without presenting any quantitative data.[43,69,70,90,104] Among the 17 studies that reported data on renal function, 2 were rated as being good-quality studies;[25,105] 5 were of poor quality;[80,88,94,99,113] 4 were nonrandomized studies;[80,99,110,113] and 5 had more than 100 patients.[25,37,59,73,105] All but seven[37,59,62,73,78,110,113] compared losartan with a specific ACEI; the ACEI most frequently studied was enalapril.[25,37,41,80,94,99] Studies comparing direct renin inhibitors with either ACEIs or ARBs also did not demonstrate differential effects related to renal function, but they were generally larger and of higher quality.[104,105]

The best comparative study assessed GFR by renal scintigraphy at baseline and after 3 years of followup.[41] The authors reported increases in mean GFR in both groups, but there was no statistically significant difference between groups. One of the larger studies in this group (n = 190) reported a greater short-term increase (12-week study) in mean serum creatinine in the enalapril group (change 0.03 mg/dL [95% CI 0 to 0.06]) compared with the irbesartan group (change 0.01 mg/dL [95% CI -0.02 to 0.04]).[59]

Among seven fair- to good-quality studies that reported on changes in renal function, all reported small differences during treatment without differences by class of angiotensin antagonist.[25,42,62,73,78,105,110] Of two poor-quality studies that reported on changes in creatinine clearance, one reported no change.[94] Although the other study reported significant and similar decreases in creatinine clearance in both groups,[88] these changes did not correspond to the changes in serum creatinine reported, which calls into question the reliability of the data. Of the two studies that reported summary data, one found a 9 percent mean decline in GFR assessed by radio-labeled excretion in each group ($p < 0.001$ at 52 weeks),[53] while the other found no change in mean percent change in serum creatinine.[75] Of the five studies that did not present detailed data, two reported that there were no overall differences between groups;[70,90] another reported that the degree and direction of insignificant change in renal function were comparable in both treatment groups;[43] and the last two described that a few patients developed an increase in serum creatinine: 2 out of 192 patients treated with losartan developed an increase in serum creatinine during the 12-week study,[69] while 3 out of 422 patients treated with ramipril developed an increase in serum creatinine during the 26-week study.[103]

Meta-Analyses of Studies Reporting Creatinine-Related Outcomes

Several studies reported pre- and post-treatment creatinine-related values. These included serum creatinine, creatinine clearance, and GFR. Using the pre- to post-treatment difference as an endpoint requires the standard deviation of the difference or the intra-class correlation. In most cases, neither was available. For this reason we chose to look at the posttreatment values without reference to the pretreatment values. We used the standardized difference in means (ARB mean minus ACEI mean) as our effect measure.

Table 10 gives a summary of the studies reporting serum creatinine and their estimated standardized mean differences. Note that when several trials assessed the same outcome using different scales, we used a standardized mean difference to convert all outcomes to a common scale, measured in units of standard deviations.

Table 10. Estimated standardized mean differences for studies reporting serum creatinine (ARB minus ACEI)

Study	Mean difference	Standard error	Variance	Study type
Avanza et al., 2000[80]	0.000	0.365	0.133	OBS
Verdecchia et al., 2000[99]	0.133	0.246	0.061	OBS
Ozturk et al, 2009[113]	0.156	0.204	.041	OBS
Fogari et al., 2002[44]	0.000	0.217	0.047	RCT
Uchiyama-Tanaka et al., 2005[77]	0.000	0.309	0.096	RCT
Hermida et al., 2008[25]	0.143	0.165	0.027	RCT
Zhu et al., 2008[78]	0.138	0.259	0.067	RCT
Nakamura et al., 2009[62]	0.190	0.275	0.076	RCT

OBS = observational study; RCT = randomized controlled trial

We summarized all studies together, as well as analyzing certain subgroups. We compared RCTs to observational studies. The results are summarized in Table 11. The analyses include measures of homogeneity (Q-statistic).

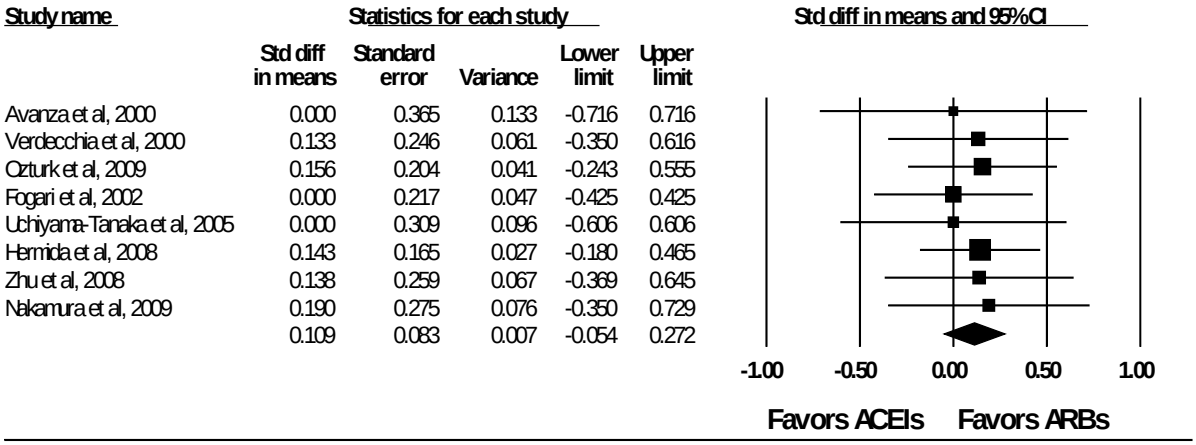
Table 11. Meta-analyses of serum creatinine by subgroup for ARB minus ACEI

Model	Analysis subgroup	No. of studies	Mean difference	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	8	0.109	-0.054	0.272	1.311	0.190	0.668	7	0.999
Random	All	8	0.109	-0.054	0.272	1.311	0.190			
Fixed	Observ	3	0.124	-0.159	0.406	0.857	0.391	0.141	2	0.763
Random	Observ	3	0.124	-0.159	0.406	0.857	0.391			
Fixed	RCT	5	0.102	-0.098	0.301	1.000	0.317	0.512	4	0.989
Random	RCT	5	0.102	-0.098	0.301	1.000	0.317			

CI = confidence interval; df = degrees of freedom; Observ = observational study; RCT = randomized controlled trial

The results for the random-effects analysis of all studies are shown in Figure 5.

Figure 5. Random-effects analysis of all studies reporting serum creatinine (ARB mean minus ACEI mean)



The analysis of all studies gave an estimated standardized mean difference of 0.109 (95 percent CI -0.054 to 0.272), suggesting that mean post-treatment creatinine levels are slightly higher for the ARB studies, but the difference is clearly not statistically significant.

Table 12 gives a summary of the studies reporting creatinine clearance and their estimated standardized mean differences.

Table 12. Estimated standardized mean differences for studies reporting creatinine clearance (ARB minus ACEI)

Study	Mean difference	Standard error	Variance	Study type
Shand et al., 2000[94]	-0.770	0.385	0.148	RCT
Kavgaci et al., 2002[88]	-0.241	0.389	0.151	RCT
Deyneli et al., 2006[42]	-0.100	0.409	0.167	RCT
Sengul et al., 2006[73]	-0.085	0.204	0.042	RCT

We summarized all studies. The results are summarized in Table 13. The analyses include measures of homogeneity (Q-statistic)

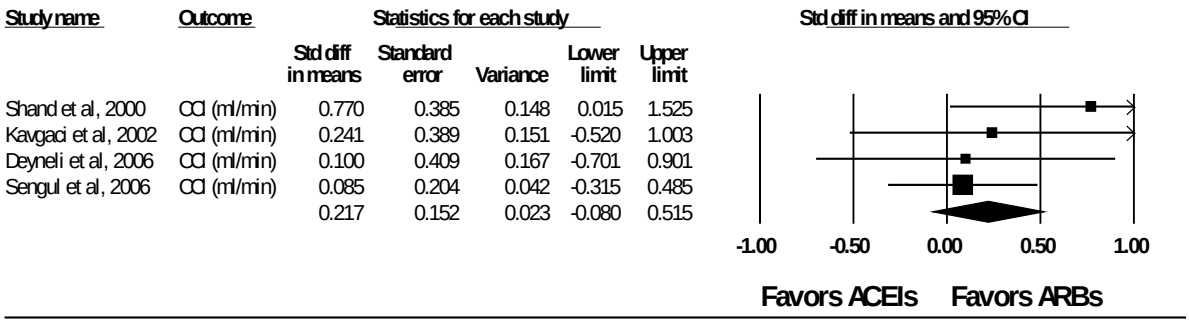
Table 13. Meta-analyses of creatinine clearance for ARB minus ACEI

Model	Analysis subgroup	No. of studies	Mean difference	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	4	-0.217	-0.515	0.080	-1.4315	0.1523	2.567	3	0.4633
Random	All	4	-0.217	-0.515	0.080	-1.4315	0.1523			

CI = confidence interval; df = degrees of freedom

The results for the random-effects analysis of all studies are shown in Figure 6.

Figure 6. Random-effects analysis of all studies reporting creatinine clearance (ARB mean minus ACEI mean)



The analysis of all studies gave an estimated standardized mean difference of 0.217 (95% CI -0.080 to 0.515), suggesting that mean post creatinine clearance levels are slightly lower for the ARB studies, but the difference is not statistically significant (p = 0.1523).

Table 14 gives a summary of the studies reporting GFR and their estimated standardized mean differences.

Table 14. Estimated standardized mean differences for studies reporting GFR (ARB minus ACEI)

Study	Mean difference	Standard error	Variance	Study type
Cotter, et al., 2008[110]	-0.608	0.245	0.060	OBS
Derosa et al., 2003[23]	-0.336	0.285	0.081	RCT
Barnett et al., 2004[37]	-0.248	0.137	0.019	RCT
Duprez, et al., 2010[105]	0.000	0.067	0.004	RCT

OBS = observational study; RCT = randomized controlled trial

We summarized all studies. The results are summarized in Table 15. The analyses include measures of homogeneity (Q-statistic).

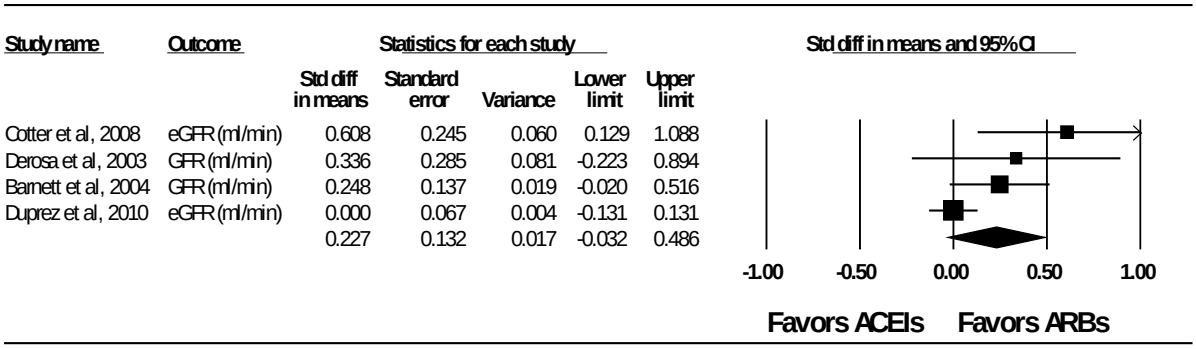
Table 15. Meta-analyses of GFR for ARB minus ACEI

Model	Analysis subgroup	No. of studies	Mean difference	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	4	-0.089	-0.201	0.022	-1.5691	0.1166	8.377	3	0.0388
Random	All	4	-0.227	-0.486	0.032	-1.7154	0.0863			

CI = confidence interval; df = degrees of freedom

The results for the random-effects analysis of all studies are shown in Figure 7.

Figure 7. Random-effects analysis of all studies reporting GFR (ARB mean minus ACEI mean)



The analysis of all studies gave an estimated standardized mean difference of 0.227 (95% CI -0.032 to 0.486), suggesting that mean post-treatment GFRs are slightly lower for the ARB studies, and the difference is marginally statistically significant (p = 0.0863).

Table 16 summarizes results for both flow rates from all studies. The analyses include measures of homogeneity (Q-statistic).

Table 16. Meta-analyses of all flow rate studies for ARB minus ACEI

Model	Analysis subgroup	No. of studies	Mean difference	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	8	-0.105	-0.210	-0.001	-1.9720	0.0486	11.566	7	0.1158
Random	All	8	-0.212	-0.396	-0.028	-2.2617	0.0237			

CI = confidence interval; df = degrees of freedom; GFR = glomerular filtration rate

The analysis of all flow studies gave an estimated standardized mean difference of -0.227 (95% CI -0.396 to -0.028), suggesting that mean flow rates are slightly lower for the ARB studies, and the difference is statistically significant (p = 0.0237).

Results for Proteinuria

The 18 studies that described changes in urine albumin or protein excretion consistently demonstrated no differential effects related to reduction of urinary protein or albumin excretion among patients with essential hypertension with use of ACEIs versus ARBs. Overall fair in quality, 16 of 18 studies reported detailed data by treatment groups, while two reported summary data in graphical format.[32,110] Among the 16 studies that reported data, 2 were rated as being good-quality studies,[23,28] 4 were of poor quality;[88,90,113,115] 2 were nonrandomized cohort studies;[113,115] and only 4 had more than 100 patients.[28,37,60,75] Various ARBs were used, including two studies with telmisartan,[37,73] four studies with candesartan,[23,60,70,115] four with losartan,[42,53,75,88] one with both candesartan and losartan,[90] and two with valsartan.[28,78] All studies assessed urinary albumin excretion except for two studies that assessed urinary protein excretion.[90,113] Studies also varied in length of followup, with only one long-term study (5 years);[37] the remainder ranged from 12 weeks to 2 years. However, despite these differences in study quality, sample size, therapeutic agents, outcome measure and length of followup, all of the studies demonstrated declines in urinary protein/albumin excretion that were similar between the ACEI and ARB groups. In the only study that described changes among patients with

essential hypertension treated with aliskiren, a greater reduction in urinary albumin to creatinine ratio was observed overall, but there were no differences among those with baseline microalbuminuria or proteinuria.[104]

Discussion

The lack of an apparent differential impact of ACEIs versus ARBs on intermediate renal parameters must be considered in light of concerns about the available literature. Some concerns may reinforce the conclusion. For example, the study by Matsuda et al.[90] provided sufficient data only on the subgroup of patients with moderate proteinuria and thus would likely favor ACEIs, yet there were no significant differential effects between the ACEI and ARB groups within the entire study sample after 48 weeks ($p > 0.5$). Numerous other studies also failed to demonstrate a differential effect. On the other hand, because duration of therapy may significantly impact the ability to observe meaningful changes in renal function or proteinuria, negative results must be interpreted with caution in studies with short-term followup.

Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?

Key Points

- Cough was more frequently observed as an adverse event in groups treated with ACEIs than in groups treated with ARBs or direct renin inhibitors.
- Withdrawals due to adverse events were modestly more frequent for groups receiving an ACEI rather than an ARB or direct renin inhibitor; this is consistent with differential rates of cough.
- No significant between-class differences were observed in the rates of any other commonly reported adverse events.
- Angioedema was not reported in the majority of studies, making it impossible to accurately characterize its frequency and timing in this population. In the studies that did report episodes of angioedema, this adverse event was observed only in patients treated with an ACEI or a direct renin inhibitor.
- Treatment adherence—in terms of pill counts in RCTs—is similarly high with both ACEIs and ARBs. However, persistence with drug therapy is generally lower with ACEIs, which may be explained largely by withdrawals due to cough (as above). None of the included direct renin inhibitor studies reported adherence or persistence.
- New cancer diagnoses were not reported in any of our included studies, and we were not able to provide further evidence on an association with ARBs, ACEIs or direct rennin inhibitors.

Safety and Adverse Events

Rates of Serious and Overall Adverse Events

Fourteen studies met our inclusion criteria and reported overall rates of serious adverse events.[25-28,51,59,69,70,79,98,103,106-108] Six of these studies were rated as good in methodological quality, seven were rated as fair, and one was poor. However, the nature of serious adverse event reporting was inconsistent, and rates of serious adverse events were low (on the order of 0 to 6

percent, depending on definition); thus, data on these events were not deemed useful for assessing a differential effect of ACEIs versus ARBs.

A potentially salient and serious adverse event, angioedema, has been reported to occur in ACEI-treated patients with much greater frequently than in ARB-treated patients.[112] However, this outcome was reported in only four studies (Table 17).[51,58,63,103] One of the reported cases occurred in a patient treated with a direct renin inhibitor; the other cases were in patients treated with an ACEI. We did not pool these studies because in studies that did not report angioedema, it was not clearly valid to infer that there were no events simply because the studies did not report explicitly that an episode of angioedema did not occur. Thus, we are unable to estimate the frequency of angioedema in this population.

Table 17. Studies reporting angioedema

Study	Study design (blinding)	Interventions (numbers of patients)	Duration	Quality	Results
Andersen et al., 2008[103]	RCT (double-blinded)	Ramipril (n = 422) Aliskiren (n = 420)	26 weeks	Good	No cases of angioneurotic edema with ramipril 1 case angioneurotic edema in one patient receiving aliskiren
Karlberg et al., 1999[51]	RCT (double-blinded)	Telmisartan (n = 139) Enalapril (n = 139)	26 weeks	Fair	No cases of angioedema with telmisartan 1 case ("severe disabling Quincke's angioneurotic edema") with enalapril
McInnes et al., 2000[58]	RCT (double-blinded)	Candesartan (n = 237) Lisinopril (n = 116)	26 weeks	Fair	No cases of angioedema with candesartan 2 cases with lisinopril
Neutel et al., 1999[63]	RCT (double-blinded)	Telmisartan (n = 385) Lisinopril (n = 193)	48 weeks	Fair	No cases of angioedema with telmisartan 2 cases with lisinopril

Of the 47 studies that met inclusion criteria and reported overall adverse event rates,[23-31,34,35,37,38,40,42,43,45,47,51,52,54,56-59,62,63,69,70,73,75,76,78,79,82,85,89,91,94,98,101,103,105-109] only 15 were assessed as being good in quality. There was significant variation across studies in the manner in which adverse events data were collected and reported. Several studies reported only "severe" or "major" adverse events, and no consistent method was used across studies to classify the severity of events. For these reasons, data on overall rates of adverse events were not considered further.

Specific Adverse Events

Forty-eight studies reported rates of one or more specific adverse events,[23-31,34,35,38,40-43,45,47,51-54,56-59,61-63,69,73,75,76,78,79,89,91,98,101,103,105-109,115-117] including cough (42 studies), dizziness (31 studies), headache (30 studies), fatigue or asthenia (17 studies), upper respiratory infection (11 studies), nausea (12 studies), diarrhea (5 studies), and dyspepsia (5 studies). Back pain and hypotension were each reported as an adverse event in four studies. Viral infection, sinusitis, peripheral edema, and nasophyrangitis were reported as adverse events by three studies each. Palpitations, myalgia, malaise, urinary tract infection, vertigo, hypertensive crisis, abnormal taste, and musculoskeletal pain were reported by two studies each. Accident/injury, pharyngitis, rhinitis, dyspnea, abdominal pain, constipation, dry mouth, feeling sick, pyrosis, insomnia, fever,

impotence, flatulence, epigastric discomfort, increased sweating, erythematous rash, flushing, cold hands/feet, atrial flutter, death, cor pulmonale, heartburn, oral erythema, instable deambulance, adverse events related to the nervous system, adverse events related to the cardiovascular system, and adverse events related to the gastrointestinal system were reported as a specific adverse events by one study each.

Given the large number of commonly reported specific adverse events, we focused on three specific events with the largest difference in absolute rates across studies: dizziness, headache, and cough. Rates of dizziness in studies reporting this event (n = 31) ranged from 1 to 20 percent in ARB-treated groups (mean 3.7 percent), from 0 to 18 percent in ACEI-treated groups (mean 4.4 percent), and from 3 to 8 percent in the three studies involving direct renin inhibitors (mean 6.0 percent). For headache (n = 30 studies), rates ranged from 1 to 22 percent in ARB-treated groups (mean 5.8 percent), from 0 to 34 percent in ACEI-treated groups (mean 7.0 percent) and 9 to 11 percent in direct renin inhibitor-treated groups (mean 10.0 percent). These results suggest that there is no differential impact of ACEIs and ARBs or direct renin inhibitors with regard to dizziness or headache.

The one adverse event for which significant differential effects were apparent is cough. Forty-two studies reported cough as an adverse event; of these, 40 studies compared cough in subjects treated with ACEIs or ARBs, and two compared cough rates in subjects treated with an ACEI or a direct renin inhibitor.[103,105] The single eligible study that compared adverse events between an ARB and a renin inhibitor[107] did not report cough as an adverse event in either treatment arm. In terms of quality, 9 of the 42 studies were rated as good, 26 as fair, and 7 as poor. Thirty-nine of the studies were RCTs, two were prospective cohort studies, and one was a cross-sectional cohort study. Sample sizes for the studies ranged from 24 to 51,410 patients, with a total of 68,875 patients. Study durations ranged from 12 weeks to 3 years. The mean patient age of study participants was 58 years. The proportion of female patients included ranged from 24 to 100 percent (mean 48 percent). Twenty-four studies (57 percent) reported the racial demographics of the study participants. Of these 24 studies, 11 (46 percent) enrolled a minimum of 10 percent of ethnic minority participants.

Rates of cough in these studies ranged from 0 to 13 percent for ARB-treated groups (mean 2.2 percent), and from 0 to 23 percent in ACEI-treated groups (mean 8.7 percent). Cough rates associated with direct renin inhibitors were 4.1 and 4.2 percent in the two studies that compared an ACEI with a direct renin inhibitor.[103,105] All 40 studies that compared cough rates between ACEI and ARB treatments demonstrated higher rates of cough in ACEI-treated participants, but statistical significance was not always reported, and the magnitude of the differences in rates were sometimes small.

For the meta-analysis of studies reporting cough as an adverse event, we included all 40 studies that reported on cough rates. Table 18 gives a summary of the studies and their estimated odds ratios. The odds ratio represents the odds of having a cough for the ARB patients divided by the odds of having a cough for the ACEI patients.

Table 18. Estimated odds ratios for cough (ARBs vs. ACEIs)

Study	Odds ratio	Ln(OR)	Standard error	Study type
Mackay et al., 1999[117]	0.284	-1.259	0.132	OBS
Gregoire et al., 2001[116]	0.300	-1.202	0.533	OBS
Sato et al., 2003[115]	0.162	-1.819	1.576	OBS
Tikkanen et al., 1995[75]	0.072	-2.631	0.742	RCT
Townsend et al., 1995[76]	0.246	-1.402	0.800	RCT
Ruff et al., 1996[29]	0.638	-0.450	0.807	RCT
Black et al., 1997[38]	0.127	-2.060	0.570	RCT
Larochelle et al., 1997[54]	0.168	-1.781	0.697	RCT
Roca-Cusachs et al., 1997[69]	0.905	-0.100	0.407	RCT
Mimran et al., 1998[59]	0.446	-0.807	0.482	RCT
Elliott, 1999[43]	0.514	-0.666	0.236	RCT
Karlberg et al., 1999[51]	0.368	-0.999	0.416	RCT
Naidoo et al., 1999[61]	0.363	-1.012	0.362	RCT
Neutel et al., 1999[63]	0.411	-0.888	0.404	RCT
Lacourciere et al., 2000[53]	0.057	-2.873	1.475	RCT
Malmqvist et al., 2000[57]	0.023	-3.761	1.437	RCT
McInnes et al., 2000[58]	0.160	-1.830	0.379	RCT
Ruilope et al., 2001[30]	0.092	-2.390	1.055	RCT
Amerena et al., 2002[35]	0.078	-2.551	0.743	RCT
Coca et al., 2002[40]	0.095	-2.349	1.058	RCT
Cuspidi et al., 2002[109]	0.275	-1.290	0.665	RCT
De Rosa et al., 2002[41]	0.280	-1.273	1.192	RCT
Ragot et al., 2002[91]	0.160	-1.834	0.770	RCT
Derosa et al., 2003[23]	0.200	-1.609	1.563	RCT
Fogari et al., 2004[45]	0.240	-1.428	1.130	RCT
Malacco et al., 2004[26]	0.129	-2.049	0.439	RCT
Koylan et al., 2005[89]	0.087	-2.446	0.613	RCT
Deyneli et al., 2006[42]	0.307	-1.182	1.683	RCT
Fogari, et al., 2006[47]	0.195	-1.635	1.557	RCT
Lacourciere et al., 2006[106]	0.028	-3.574	1.018	RCT
Tedesco et al., 2006[34]	0.108	-2.226	1.496	RCT
Williams et al., 2006[108]	0.084	-2.478	0.741	RCT
Xu et al., 2007[101]	0.209	-1.567	1.563	RCT
Fogari et al., 2008[24]	0.109	-2.214	1.496	RCT
Kloner et al., 2008[52]	0.150	-1.898	1.518	RCT
Zhu et al., 2008[78]	0.187	-1.677	1.571	RCT
Nakamura et al., 2009[62]	0.192	-1.648	1.574	RCT
Spinar et al., 2009[98]	0.122	-2.105	0.530	RCT
Akat et al., 2010[79]	.099	-2.317	1.511	RCT
Malacco et al., 2010[27]	0.152	-1.884	0.762	RCT

Ln(OR) = natural log of odds ratio; OBS = observational study; RCT = randomized controlled trial

We summarized all studies, as well as comparing RCTs to observational studies. The results are summarized in Table 19. The analyses include measures of homogeneity (Q-statistic).

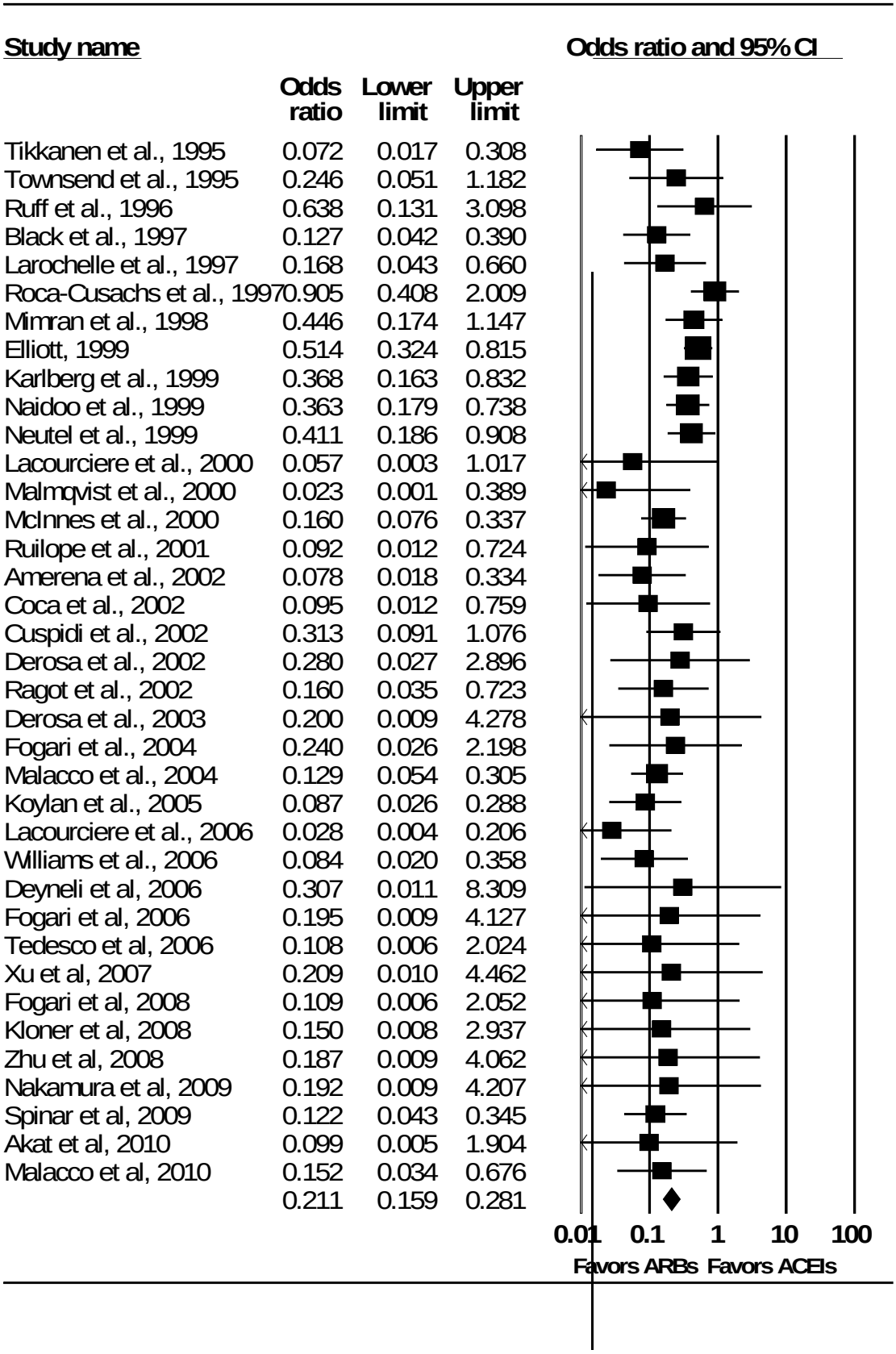
Table 19. Meta-analyses of cough by subgroup for ARBs versus ACEIs

Model	Analysis subgroup	No. of studies	OR estimate	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	40	0.268	0.229	0.313	-16.473	0.0000	55.770	39	0.040
Random	All	40	0.228	0.180	0.290	-12.115	0.0000	-	-	-
Fixed	Observ	3	0.284	0.221	0.365	-9.841	0.0000	0.137	2	0.934
Random	Observ	3	0.284	0.221	0.365	-9.841	0.0000	-	-	-
Fixed	RCTs	37	0.257	0.211	0.315	-13.224	0.0000	55.276	36	0.021
Random	RCTs	37	0.210	0.158	0.279	-10.713	0.0000	-	-	-

CI = confidence interval; df = degrees of freedom; Observ = observational studies; OR = odds ratio; RCTs = randomized controlled trials

The results for the random-effects analysis of RCTs are in Figure 8. Analysis of the potential for publication bias is provided in Appendix H.

Figure 8. Random-effects analysis of RCTs for cough (ARBs vs. ACEIs)



The results are best summarized by the random-effects analysis of the RCTs. This analysis gave an estimated odds ratio of 0.211 (95% CI 0.159 to 0.281) suggesting that the odds of having a cough is only one-fifth as large with an ARB as it is with an ACEI.

These odds ratios need to be compared against the overall cough rate for ACEIs. The Mackay et al. observational study[117] (which is by far the largest study) would suggest that this rate is about 1.5 percent. If we pool all of the RCTs, we get a rate of about 9.9 percent.

There were two studies (both RCTs) comparing a direct renin inhibitor with an ACEI. Their results are summarized in Table 20.

Table 20. Meta-analyses of cough for direct renin inhibitors vs. ACEIs

Model	Analysis subgroup	No. of studies	OR estimate	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	RCTs	2	0.3325	0.2241	0.4933	-5.4704	0.0000	0.7622	1	0.3826
Random	RCTs	2	0.3325	0.2241	0.4933	-5.4704	0.0000	-	-	-

CI = confidence interval; df = degrees of freedom; OR = odds ratio; RCTs = randomized controlled trials

This analysis gave an estimated odds ratio of 0.333 (95 percent CI 0.2241 to 0.4933), suggesting that the odds of having a cough is only one-third as large with a direct renin inhibitor as it is with an ACEI.

Withdrawals Due to Adverse Events

Forty-one studies met our inclusion criteria and reported withdrawals due to adverse events.[24-28,31-35,37,38,40-43,47,51-53,56,58-63,69,75,76,78,80,89,94,99,101,103,105-107,109] Of these, 12 (29 percent) were of good methodological quality, 24 (59 percent) were fair in quality, and 5 (12 percent) were poor. Thirty-nine studies were RCTs, one was a nonrandomized controlled clinical trial, and one was a case-control study. Sample sizes for the individual studies ranged from 46 to 1,213 patients, with a total of 13,286 patients. Study durations ranged from 12 weeks to 5 years. The proportion of female patients included ranged from 24 to 100 percent (mean 48 percent). Twenty-one studies (51 percent) reported the racial demographics of the study participants. Ten of these (24 percent of the 41 total studies) enrolled a minimum of 10 percent of ethnic minority participants, while 6 enrolled only white patients.

Rates of withdrawals due to adverse events ranged from 1 to 20 percent, with a mean of 3 percent for patients on ARBs, and a mean of 5.5 percent for patients on ACEIs. Thirty-six trials reported withdrawals due to adverse events for both ACEIs and ARBs; in 28 of these trials (78 percent) there were more withdrawals in the ACEI-treated groups. However, there was significant variation in the study protocols and data reporting.

We conducted a meta-analysis of the 36 studies that reported withdrawals due to adverse events for both ACEIs and ARBs. Table 21 gives a summary of the studies and their estimated odds ratios. The odds ratio represents the odds of withdrawing for the ARB patients divided by the odds of withdrawing for the ACEI.

Table 21. Estimated odds ratios for withdrawals due to adverse events (ARBs vs. ACEIs)

Study	Odds ratio	Ln(OR)	Standard error	Study type
Avanza et al., 2000[80]	0.2635	-1.3337	1.5177	OBS
Verdecchia et al., 2000[99]	0.4500	-0.7985	0.8074	OBS
Mallion et al., 1995[56]	0.9899	-0.0102	0.5749	RCT
Tikkanen et al., 1995[75]	0.4176	-0.8731	0.4984	RCT
Townsend et al., 1995[76]	0.7561	-0.2796	0.4590	RCT
Black et al., 1997[38]	0.8950	-0.1109	0.4526	RCT
Roca-Cusachs et al., 1997[69]	0.4128	-0.8849	0.6004	RCT
Mimran et al., 1998[59]	3.1895	1.1599	1.1635	RCT
Elliott, 1999[43]	1.0000	0.0000	1.4169	RCT
Karlberg et al., 1999[51]	0.6606	-0.4145	0.4115	RCT
Naidoo et al., 1999[61]	0.9827	-0.0175	0.8236	RCT
Neutel et al., 1999[63]	0.0602	-2.8097	1.0644	RCT
Lacourciere et al., 2000[53]	2.0000	0.6931	1.2410	RCT
McInnes et al., 2000[58]	0.4574	-0.7822	0.3964	RCT
Mogensen et al., 2000[60]	0.9688	-0.0317	1.0158	RCT
Shand et al., 2000[94]	0.2903	-1.2368	1.6749	RCT
Amerena et al., 2002[35]	0.4808	-0.7324	0.6187	RCT
Coca et al., 2002[40]	0.6850	-0.3783	0.9227	RCT
Cuspidi et al., 2002[109]	0.4700	-0.7550	0.5116	RCT
De Rosa et al., 2002[41]	0.1159	-2.1550	1.5395	RCT
Barnett et al., 2004[37]	0.6667	-0.4055	0.3215	RCT
Malacco et al., 2004[26]	0.3854	-0.9535	0.3975	RCT
Koylan et al., 2005[89]	0.0174	-4.0531	1.4315	RCT
Schram et al., 2005[32]	3.0000	1.0986	1.1952	RCT
Deyneli et al., 2006[42]	0.3067	-1.1820	1.6833	RCT
Fogari, et al., 2006[47]	0.4872	-0.7191	0.8809	RCT
Lacourciere et al., 2006[106]	0.5098	-0.6738	0.3633	RCT
Spoelstra-de Man et al., 2006[33]	3.0000	1.0986	1.1952	RCT
Tedesco et al., 2006[34]	0.3937	-0.9322	0.8461	RCT
Xu et al., 2007[101]	0.2086	-1.5673	1.5627	RCT
Fogari et al., 2008[24]	0.1967	-1.6261	1.1030	RCT
Hermida et al., 2008[25]	2.0000	0.6931	1.2353	RCT
Kloner et al., 2008[52]	0.3561	-1.0326	1.6388	RCT
Menne et al., 2008[28]	0.8063	-0.2154	0.7947	RCT
Zhu et al., 2008[78]	0.1869	-1.6773	1.5709	RCT
Nakamura et al., 2009[62]	0.1925	-1.6479	1.5738	RCT

Ln(OR) = natural log of odds ratio; OBS = observational study; RCT = randomized controlled trial

We summarized all studies, as well as comparing RCTs to observational studies. The results are summarized in Table 22. The analyses include measures of homogeneity (Q-statistic). Analysis of the potential for publication bias is provided in Appendix H.

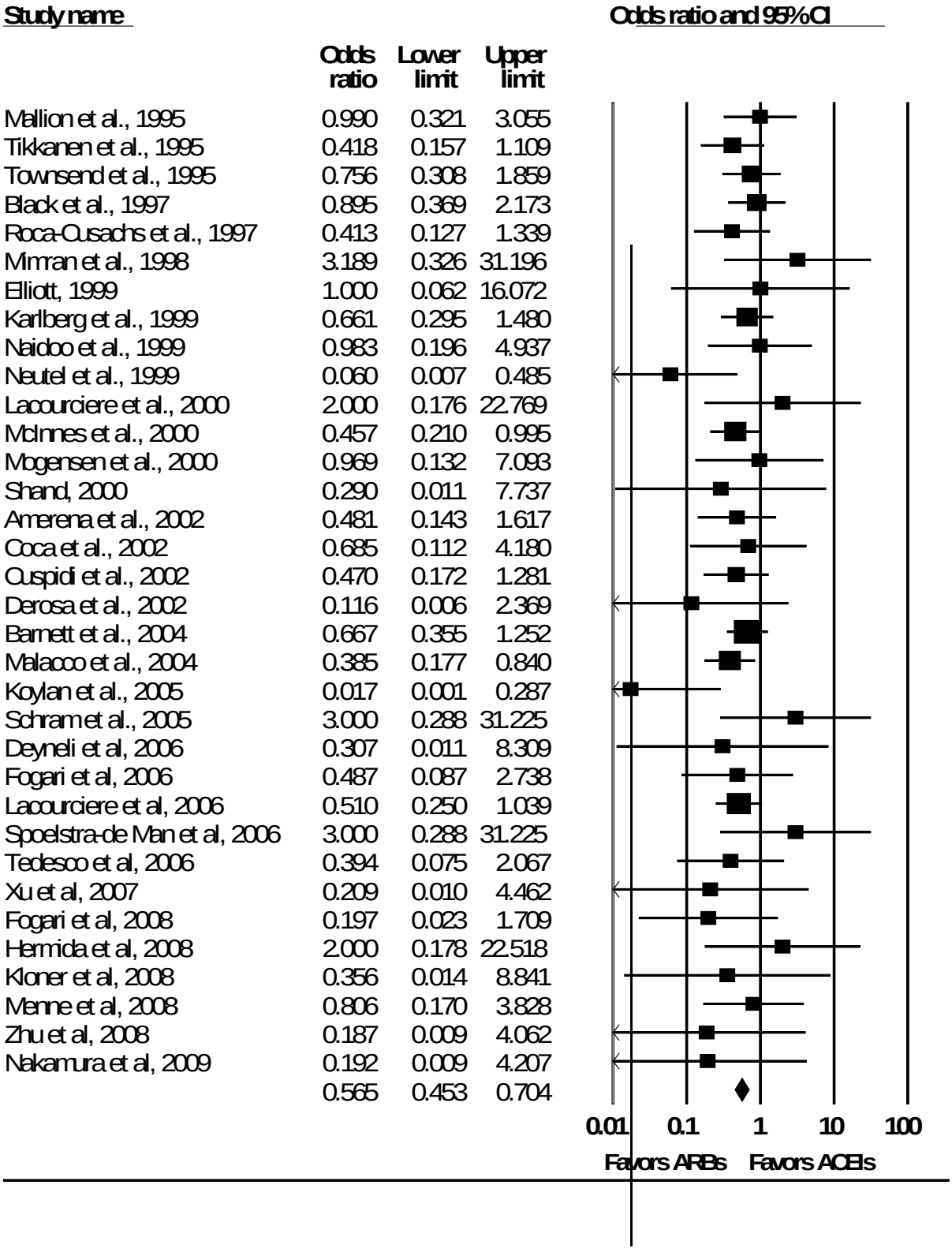
Table 22. Meta-analyses of withdrawals due to adverse events by subgroup for ARBs vs. ACEIs

Model	Analysis subgroup	No. of studies	OR estimate	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	36	0.5599	0.4500	0.6966	-5.2027	0.0000	28.8562	35	0.7584
Random	All	36	0.5599	0.4500	0.6966	-5.2027	0.0000	-	-	-
Fixed	Obs	2	0.3999	0.0989	1.6169	-1.2859	0.1985	0.0969	1	0.7555
Random	Obs	2	0.3999	0.0989	1.6169	-1.2859	0.1985	-	-	-
Fixed	RCTs	34	0.5646	0.4526	0.7044	-5.0639	0.0000	28.5308	33	0.6893
Random	RCTs	34	0.5646	0.4526	0.7044	-5.0639	0.0000	-	-	-

CI = confidence interval; df = degrees of freedom; OR = odds ratio; Obs = observational studies; RCTs = randomized controlled trials

The results for the random-effects analysis of RCTs are shown in Figure 9.

Figure 9. Random-effects analysis of RCTs for withdrawals due to adverse events (ARBs vs. ACEIs)



The results are best summarized by the random-effects analysis of the RCTs. This analysis gave an estimated odds ratio of 0.565 (95% CI 0.453 to 0.704), suggesting that the odds of withdrawing due to an adverse event are only 56 percent as large with an ARB as with an ACEI.

These odds ratios need to be compared against the overall withdrawal rate for ACEIs. If we pool all of the RCTs, we get a rate of about 5.4 percent.

There were two studies (both RCTs) comparing a direct rennin inhibitor with an ACEI. Their results are summarized in Table 23.

Table 23. Meta-analyses of withdrawals due to adverse events for direct renin inhibitors vs. ACEIs

Model	Analysis subgroup	No. of studies	OR estimate	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	RCTs	2	0.8282	0.5747	1.1935	-1.0113	0.3119	2.9951	1	0.0835
Random	RCTs	2	0.8861	0.4581	1.7136	-0.3595	0.7193	-	-	-

CI = confidence interval; df = degrees of freedom; OR = odds ratio; RCTs = randomized controlled trials

This analysis gave an estimated odds ratio of 0.886 (95% CI of 0.458, 1.714), suggesting that the estimated odds of withdrawing due to adverse events is only 89 percent as large with a direct renin inhibitor as it is with an ACEI, but this value is not significantly different from 1.00 (100 percent).

Caveats and concerns in relation to these data include the fact that only 9 of the 40 studies were considered to be of good methodological quality. Also, there was significant heterogeneity in the reporting of withdrawal data. Many studies reported limited data on withdrawal rates. Moreover, only one trial analyzed data to assess variation in withdrawal rates by specific demographic subgroups.[117]

Adherence and Persistence

Forty-one papers describing 39 distinct studies reported at least some quantitative information on persistence or adherence[24,25,28,33-35,40,42,47,49,50,52,57,58,62,70,71,73,78,89,100,101,103,105-108,114,118-130] Studies of adherence consisted of RCTs that assessed reported pill counts or subject dropout. Since subject dropout did not uniformly reflect adherence with medication (as opposed to adherence with the study protocol, for example), we focused on the nine studies that measured pill counts. Seventeen studies of persistence – whether patients remain on the initial ACEI, ARB, or direct renin inhibitor – included 4 RCTs as well as 13 longitudinal cohorts in which patients were followed in a real-world setting. Two studies evaluated adherence to an ACEI versus a direct renin inhibitor, and one evaluated adherence to an ARB versus a direct renin inhibitor. All the other studies compared ACEIs to ARBs. While adherence and persistence were lower in cohort studies than in the randomized trials, the general conclusions from the two groups of studies were similar.

With the possible exception of the study by Koylan et al.,[89] adherence with ACEIs and ARBs was similar (Table 24). Moreover, adherence was high: above 90 percent in all studies, and at least 97 percent in five of the nine studies assessed. Most studies appeared to define adherence as the percentage of patients taking approximately 100 percent of the prescribed pills, although not every article was precise in reporting how this figure was derived. The absolute magnitude of adherence depended on the width of the acceptable range (e.g., McInnes et al.[58] used a narrow range of 90 to 110 percent of prescribed pills and so might be expected to report lower adherence than Malmqvist et al.,[57] which considered a wider range of 75 to 125 percent of prescribed pills

to be acceptable). Also, randomized trials, which engender such biases as motivated volunteers and a Hawthorne effect, will tend to overestimate adherence in comparison with usual practice. Nevertheless, the overall conclusion that adherence was good and similar between ACEIs and ARBs seems well supported.

Table 24. Studies of treatment adherence with ACEIs and ARBs

Study	Adherence with ACEIs	Adherence with ARBs	Definition of adherence
Amerena et al., 2002[35]	99%	99%	Pill counts at 6 weeks
	98%	98%	Pill counts at 12 weeks
Coca et al., 2002[40]	98.4%	98.3%	Taking 80-110% of pills
Fogari et al., 2006[47]	92%	94%	Pill count at each study visit
Koylan et al., 2005[89]	~ 94%	~ 96%	Taking pills daily at 1 month visit
	~ 86%	~ 96%	Taking pills daily at 3 month visit
	~ 87%	~ 96%	Taking pills daily at 6 month visit
Malmqvist et al., 2000[57]	> 98%	> 98%	Taking 75-125% of pills at 6 weeks
	> 98%	> 98%	Taking 75-125% of pills at 12 weeks
McInnes et al., 2000[58]	90%	90%	Taking 90-110% of pills
Rosei et al., 2005[70]	98.2%	97.8%	Not specifically defined
Tedesco et al., 2006[34]	> 90%	> 90%	Pill count at study visits
Williams et al., 2006[108]	> 98.8%	> 98.8%	Taking 80-120% of pills

Regarding persistence, the majority of evidence came from nonexperimental studies, which are subject to a variety of caveats, described below. These caveats notwithstanding, the results were quite consistent in that persistence with ARBs was modestly better than persistence with ACEIs (Table 25). Noting both the consistency of this finding across studies and the rather modest degree of differences in persistence, the conclusion that ARBs exhibit somewhat better persistence than ACEIs can be drawn with a moderate degree of confidence. No study reported persistence associated with direct renin inhibitor treatment.

Table 25. Studies of persistence with ACEIs and ARBs

Study	Duration	ACEIs			ARBs		
		Continued	Switched	Discontinued	Continued	Switched	Discontinued
Randomized trials							
Saito et al., 2004[71]	6 mo	71%	28%	2%	89%	9%	2%
Koylan et al., 2005[89]	6 mo	~ 82%	-	-	~ 89%	-	-
Hosohata et al., 2007[50]	12 mo	55%	-	-	88%	-	-
Veronesi et al.,2007[100]	24 mo	61.5%	-	-	68.5%	-	-
Longitudinal cohort studies							
Hasford et al., 2002[49]	1 yr	42%	-	-	44.7 to 60.8%	-	-
Mazzaglia et al., 2005[114]	1 yr	~ 50%	~ 8%	~ 42%	~ 50%	~ 10%	~ 40%
Bloom et al., 1998[118]/Conlin et al., 2001[121]	1 yr	58%	9%	33%	64%	7%	29%
	4 yr	46.5%	18.9%	34.6%	50.8%	16.5%	32.7%
Erkens et al., 2005[124]	1 yr	59.7%	-	-	62.0%	-	-
Marentette et al., 2002[125]	1 yr	-	-	~ 35%	-	-	~ 15%
Bourgault et al., 2005[119]	1 yr	-	-	41%	-	-	34%
	2 yr	-	-	53%	-	-	44%
	3 yr	-	-	60%	-	-	47%
Burke et al., 2006[120]	1 yr	-	-	37.8%	-	-	29.4%
	2 yr	-	-	48.0%	-	-	41.3%
	3 yr	-	-	54.8%	-	-	50.3%
	4 yr	-	-	60.4%	-	-	57.8%
Wogen et al., 2003[126]	1 yr	50%	-	-	63%	-	-
Degli Esposti et al., 2002[122,123]	1 yr	30.7%	9.4%	59.9%	33.4%	24.6%	42.0%
Hasford et al., 2007[127]	1 yr	28.2%	-	-	26.4%	-	-
	2 yr	18.6%	-	-	15.3%	-	-
	3 yr	14.0%	-	-	10.6%	-	-
Patel et al., 2007[129]	1 yr	48.0%	-	-	51.9%	-	-
Lachaine et al., 2008[128]	2 yr	58.9%	-	-	60.9%	-	-
Simons et al., 2008[130]	33 mo	45% (95% CI 44 to 46%)	-	-	47% (95% CI 46 to 48%)	-	-

The results of the longitudinal studies should be considered in light of several caveats. The longitudinal cohort studies typically use administrative databases and, even though investigators control for differing patient characteristics as much as possible, this design cannot assure that patients receiving different medications are similar, even after statistical adjustment. Consequently, the consistency of results across multiple studies is crucial. Results of multi-predictor analyses, when present, yielded substantially similar conclusions to the simple comparison of unadjusted persistence provided above; accordingly, we focus on the unadjusted results.

The ideal outcome would disaggregate patients into four mutually exclusive and exhaustive categories: (1) continued initial medication without change; (2) continued initial medication but added another medication from a different class; (3) changed to another medication from a

different class; and (4) discontinued medication entirely. Almost all of the reports aggregated the first two categories, which we have combined throughout. Within each category, definitions are not entirely consistent, but are close enough for purposes of comparison.

As a final caveat, several of the longitudinal cohort studies (e.g., Marentette et al.,[125] Bourgault et al.,[119] Burke et al.,[120] Wogen et al.,[126] and Degli Esposti et al.[122,123]) corresponded in time to the introduction of ARBs, and thus have relatively small sample sizes for this class of medication. Accordingly, for these studies persistence is estimated with less precision than might be desired.

Key Question 3. Are there subgroups of patients—based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent us of other medications)—for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?

Key Points

- Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs, ARBs, and direct renin inhibitors for any particular patient subgroup.

Blood Pressure

Comparisons of ACEIs Versus ARBs

We did not identify any subgroup of patients in whom one ACEI or ARB was clearly superior. Two of 78 studies reporting blood pressure outcomes included only women,[46,57] and 2 additional studies reported results for a female subgroup.[51,56] Three of these four found no significant difference in blood pressure effects between the ACEI and the ARB treatment arms; however, the largest of the four[57] reported superior blood pressure lowering in the ARB arm compared to the ACEI ($n = 286$, mean between group difference 5.5/2.2 mm Hg; $p \leq 0.01$). There were five studies conducted exclusively in elderly patients (age $\geq$ 65), and three additional studies that reported separate results for this age group.[27,30,36,45,51,56,76,84] Five of these studies showed no difference between ACEI and ARB treatment in elderly patients,[30,36,51,56,84] and the remaining three studies reported better blood pressure lowering in the ARB arm.[27,45,76] Ten studies were conducted only in diabetic patients with hypertension, none of which showed a difference between the two classes of medication.[23,32,37,44,52,53,60,70,83,88] In four studies, blood pressure was reported as an outcome in a subgroup of black patients.[29,55,61,76] Three of these studies found no difference in the efficacy of ACEIs versus ARBs in black patients, while one reported significantly better DBP lowering in ARB-treated patients compared to ACEI-treated patients.[76]

Comparisons of Direct Renin Inhibitors Versus ACEIs or ARBs

Of the three studies comparing the direct renin inhibitor aliskiren to an ACEI or ARB, one was conducted solely in patients over age 65.[105] Aliskiren provided greater blood pressure lowering than the ACEI ramipril; however, this result was also reported in a similar study comparing aliskiren and ramipril, which was not restricted to patients over age 65 (two publications[103,104]), suggesting that this effect is unlikely to be unique to an elderly subgroup.

Mortality and Major Cardiovascular Events

Because of scant data on mortality, MI, and stroke, it was not possible to assess whether ACEIs and ARBs have any differential effect on event rates in any subgroups of patients based on demographic characteristics, use of other medications concurrently, or comorbidities.

Quality of Life

None of the included trials reported any differential impact of ACEIs versus ARBs (or versus direct renin inhibitors) on quality-of-life measures by clinically relevant subgroup.

Safety and Adverse Events

In general, there is no evidence supporting differential rates of adverse events for ACEIs versus ARBs or direct renin inhibitors with regard to any specific subgroup. However, one study included only women in the study population.[57] The overall rates of cough reported by the study were similar to those reported by other studies that included men and women. One study reported results for a female subgroup.[117] The proportion of women in the latter study was 55.7 percent, and rates of cough in this study were higher for women treated with ACEIs (statistically significant for two of the three ACEIs studied in the trial) than they were for women treated with ARBs.

Prior studies not included in this review have reported a relative risk of angioedema of approximately 3 to 4 for African-Americans treated with an ACEI versus Caucasians treated with an ACEI.[131,132] In the studies we reviewed for the present report, rates of angioedema were too low to confirm this finding for ACEIs or to identify any subgroup differences across the three different medication classes.

Adherence and Persistence

There is not sufficient evidence that particular patient subgroups are more or less likely to be persistent in taking an ACEI versus an ARB, and we did not identify any studies on persistence that included patients taking a direct renin inhibitor. However, some observations emerge regarding persistence with ACEIs or ARBs (Table 26). The most consistent result is that persistence increased with age: patients in the 65- to 84-year-old age range tended to exhibit the highest persistence of all. The contribution of sex was inconsistent. There is some evidence that a history of cardiovascular disease is associated with greater persistence, a possible explanation being that such a history could make hypertension management more salient to the patient.

Table 26. Predictors of persistence with ACEIs and ARBs

Study	Predictors of persistence
Mazzaglia et al., 2005[114]	Increasing age, family history of cardiovascular diseases and diabetes, no severe hypertension, low chronic disease score
Bloom et al., 1998[118] (1yr)/Conlin et al., 2001[121] (4 yr)	1 yr: Increasing age, < 1 dose per day, male sex 4 yr: Increasing age, female sex
Erkens et al., 2005[124]	Increasing age, male sex, antidiabetic drugs, lipid lowering drugs, previous cardiovascular hospitalizations
Marentette et al., 2002[125]	Increasing age, female sex
Degli Esposti et al.,2002[123] (1 yr)/Degli Esposti et al., 2002[122] (3 yr)	1 yr: Increasing age, medications for heart disease or diabetes, previous cardiovascular hospitalizations, ≥ 2 comorbidities 3 yr: Increasing age, male sex, younger general practitioner, male sex of general practitioner
Simons et al. , 2008[130]	Age < 40 years associated with lowest persistence (16% persistence, and 3 months median persistence time) Age 60-69 years associated with highest persistence (50% persistence, and 33 months median persistence time) No significant difference by sex

Lipids

Several potentially relevant subgroups were identified, but none had a clear difference between the compared medications in lipid parameter outcomes. Six studies evaluated patients with diabetes.[23,32,44,53,60,88] These included three that found small changes in various lipid parameters,[23,53,88] but the other three found none.[32,44,60] Another study examined patients with hypertension and components of the metabolic syndrome (at least two of: high triglycerides, low HDL, high blood glucose, or high waist circumference); it found improvements in TC, TG, HDL, and LDL for ramipril and valsartan, but no differences between the medications.[102] One study targeting postmenopausal women,[46] one taking place in Japan,[77] and two taking place in Turkey[73,88] did not have detectable changes in the lipid profile. Another study taking place in Turkey[102] found improvement in all lipid parameters with both ramipril and valsartan, while another study taking place in China[101] found greater improvements in TG and HDL with telmisartan than with enalapril.

Diabetes Markers

In the eight studies requiring diabetes as an inclusion criteria, six found no difference in individuals receiving ACEIs or ARBs in glucose or HbA1c levels;[32,44,60,73,88,113] one found no change in glucose but a small statistically significant increase in HbA1c for the ARB (+ 0.25 percent enalapril, + 0.6 percent losartan; data not reported for between-group comparisons);[53] and one found no change in HbA1c but a decline in glucose levels for both which was statistically greater for the ACEI when measured at 12 months (perindopril -15 ± 4 mg/dL, candesartan -8 ± 2 mg/dL).[23] Thus, for the two studies for which a difference was found, the difference was discrepant (i.e., an increase in HbA1c in one and a decline in glucose in the other), and only one directly analyzed differences between the two groups.

In addition to studies of individuals with diabetes, measures of glucose or HbA1c were performed for several other subgroups including Asians,[62,77,96,101] Turks,[73,88,102,113] Brazilians,[80] Portuguese,[110] Spaniards,[25] Argentineans,[72] Czechs,[98] and postmenopausal women.[46] None of

these studies identified a difference in the impact of ACEIs and ARBs with regard to fasting glucose or HbA1c.

LV Mass/Function

Although 10 of the 13 studies that presented results on LV mass or function demonstrated some decreases in LVMI (or equivalent measure), the sum of the evidence does not demonstrate a difference between ACEIs, ARBs, and direct renin inhibitors with regard to their effect on LV mass or function for individuals with essential hypertension. No subgroup analyses were performed by study investigators to help identify subgroups of patients who were more likely to have improvements in LV mass or function in any of the studies.

GFR/Proteinuria

There are no consistently demonstrated differential effects with use of ACEIs, ARBs, or direct renin inhibitors related to either renal function (as measured by creatinine or GFR) or reduction of urinary protein or albumin excretion. As a result, we were not able to identify subgroups of patients for whom either ACEIs or ARBs are more effective in preserving renal function or decreasing urinary protein or albumin excretion, or are better tolerated without causing sustained elevations in serum creatinine.

Summary and Discussion

A succinct summary of the results of this review of the comparative long-term benefits and harms of angiotensin-converting enzyme inhibitor(s) (ACEIs), angiotensin II receptor blocker(s)/antagonist(s) (ARBs), or direct renin inhibitors for adults with essential hypertension is provided in three tables. First, we give an aggregated view of the strength of evidence and brief conclusions (Table 27). Second, we further describe the nature and quality of the evidence (Table 28). Finally, we summarize the quantitative analyses of outcomes, offering an estimate of the comparative outcomes for ACEIs (Table 29).

Table 27. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for essential hypertension

Key question	Strength of evidence	Conclusions
Key Question 1. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in the following health outcomes:		
a. Blood pressure control?	High (ACEI vs. ARB); Low (DRI vs. ACEI or ARB)	ACEIs and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. This conclusion is based on evidence from 77 studies (70 RCTs, 5 nonrandomized controlled clinical trials, 1 retrospective cohort study, and 1 case-control study) in which 26,170 patients receiving an ACEI or an ARB were followed for periods from 12 weeks to 5 years (median 24 weeks). Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols. Evidence concerning the effect of direct renin inhibitors on blood pressure is very limited and currently based on only three studies. These studies found the direct renin inhibitor to have a greater reduction in blood pressure compared to the ACEI ramipril (two studies) and no significant difference compared to the ARB losartan (one study).
b. Mortality and major cardiovascular events?	Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	Due to low numbers of deaths or major cardiovascular events reported, it was difficult to discern any differential effect of ACEIs versus ARBs versus direct renin inhibitors with any certainty for these critical outcomes. In 21 studies that reported mortality, MI, or clinical stroke as outcomes among 38,589 subjects, there were 38 deaths and 13 strokes reported. This may reflect low event rates among otherwise healthy patients and relatively few studies with extended followup. Only 3 of these 21 studies (including 1 death) evaluated direct renin inhibitors versus ACEIs or ARBs, and therefore the evidence to discern any differential effects between these drug classes on mortality and major cardiovascular events was insufficient.

Table 27. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for essential hypertension (continued)

Key question	Strength of evidence	Conclusions
c. Quality of life?	Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	No differences were found between ACEIs and ARBs in measures of general quality of life; this is based on four studies, two of which did not provide quantitative data. No study evaluated the comparative effectiveness of direct renin inhibitors for quality-of-life outcomes.
d. Rate of use of a single antihypertensive medication?	High (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	There was no statistically evident difference in the rate of treatment success based on use of a single antihypertensive for ARBs compared to ACEIs. The trend toward less frequent addition of a second agent to an ARB was heavily influenced by retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients, and by RCTs with very loosely defined protocols for medication titration and switching. There were no relevant studies evaluating direct renin inhibitors.
e. Risk factor reduction and other intermediate outcomes?	Lipid levels, markers of carbohydrate metabolism/ diabetes control, progression of renal disease: Moderate (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB) Progression to type 2 diabetes and LV mass/function: Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	There were no consistent differential effects of ACEIs, ARBs, on several potentially important clinical outcomes, including lipid levels and markers of carbohydrate metabolism/diabetes control. There appears to be a small difference in change in renal function between ACEIs and ARBs (favoring ACEIs), but this difference is both small and most likely not clinically meaningful or significant. Relatively few studies assessed these outcomes over the long term. There were no studies that evaluated these outcomes in direct renin inhibitors. There was no evidence for an impact of ACEIs, ARBs, or direct renin inhibitors on glucose or A1c, and no included studies evaluated rates of progression to type 2 diabetes mellitus. Although we included 13 studies of LV mass/function, these were dominated by poor-quality studies with small sample sizes, and only one study included evaluation of a direct renin inhibitor.

Table 27. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for essential hypertension (continued)

Key question	Strength of evidence	Conclusions
Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?	Cough: High (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	ACEIs have been consistently shown to be associated with greater risk of cough than ARBs (odds ratio 0.211; 95% CI 0.159 to 0.281). For RCTs, this translates to a difference in rates of cough of 7.8 percent; however, for cohort studies with lower rates of cough, this translates to a difference of 1.2 percent. There were only two studies comparing direct renin inhibitors to ACEIs and these gave an estimated odds ratio of 0.333 (95% CI of 0.2241 to 0.4933).
	Withdrawals due to adverse events: High (ACEI vs. ARB); Low (DRI vs. ACEI or ARB)	The withdrawal rate for ARBs was found to have an estimated odds ratio of 0.565 (95% CI 0.453 to 0.704) compared with ACEIs. For RCTs, this translated to an absolute difference in withdrawals of 2.3 percent (5.4% versus 3.1%). The direct renin inhibitor trials did not find a statistically significant difference (odds ratio 0.886; 95% CI 0.458 to 1.714) when compared with the withdrawal rate associated with ACEIs. There was no evidence of differences across treatments in rates of other commonly reported specific adverse events.
	Angioedema: Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	Although several studies collected data on angioedema, the event rates were very low or zero for all studies; this limited our ability to accurately characterize the frequency of angioedema. In the four studies that did report episodes of angioedema, this adverse event was observed only in patients treated with an ACEI (five patients from three studies) or a direct renin inhibitor (one patient in one study).
	Persistence with drug therapy/ treatment adherence: Moderate (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)	ACEIs and ARBs have similar rates of treatment adherence based on pill counts; this result may not be applicable outside the clinical trial setting. Rates of continuation with therapy appear to be somewhat better with ARBs than with ACEIs; however, due to variability in definitions, limitations inherent in longitudinal cohort studies, and relatively small sample sizes for ARBs, the precise magnitude of this effect is difficult to quantify. The three included studies evaluating direct renin inhibitors did not find evidence of differences in treatment adherence compared with ACEIs or ARBs. Persistence was not evaluated in any of the studies including direct renin inhibitors.

Table 27. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for essential hypertension (continued)

Key question	Strength of evidence	Conclusions
Key Question 3. Are there subgroups of patients – based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications) – a for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?	Insufficient (ACEI vs. ARB; DRI vs. ACEI or ARB)	Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs, ARBs, and direct renin inhibitors for any particular patient subgroup.

ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CI = confidence interval; GFR = glomerular filtration rate; LV = left ventricular; MI = myocardial infarction; RCTs = randomized controlled trials

Table 28. Quality of evidence summary table*

Studies	Design	Quality	Consistency	Directness	SD	SA	DR	PC
Outcome: Blood pressure control								
70	RCTs	Confounded by additional treatments, dose escalation	Consistent results	Direct	-	-	-	-
7	5 nonrandomized controlled trials, 1 cohort study, 1 case-control	Confounded by additional treatments, dose escalation	Consistent results	Direct	-	-	-	-
Outcome: Mortality and major cardiovascular events								
17	RCTs	No serious limitations	Consistent results	Direct	+	-	-	-
4	1 prospective observational study, 3 retrospective studies	Limitations based on study design	Consistent results	Direct	+	-	-	-
Outcome: Morbidity/quality of life								
4	RCTs	No serious limitations	Consistent results	Direct	-	-	-	-
Outcome: Safety (serious and overall adverse events, withdrawals due to adverse events)								
12 – serious AEs 45 – overall AEs 39 – withdrawals due to AEs	RCTs	Variation in study protocols and data reporting	Consistent results	Direct	-	-	-	-
2 – overall AEs 2 – withdrawals due to AEs	1 nonrandomized controlled trial; 1 case-control	Limitations based on study design	Consistent results	Direct	+	-	-	-

Table 28. Quality of evidence summary table* (continued)

Studies	Design	Quality	Consistency	Directness	SD	SA	DR	PC
Outcome: Specific adverse events								
45	RCTs	Variation in data reporting	Consistent results	Direct	-	-	-	-
3	3 cohort studies	Limitations based on study design	Consistent results	Direct	+	-	-	-
Outcome: Persistence with drug therapy/treatment adherence								
26	RCTs	Variation in data reporting	Consistent results	Direct	-	-	-	-
13	13 cohort studies	Limitations based on study design	Consistent results	Direct	-	-	-	-
Outcome: Rate of use of a single agent for blood pressure control								
23	RCTs	No serious flaws	Consistent results	Direct	-	-	-	-
3	2 cohort studies, 1 case-control	Limitations based on study design	Consistent results	Direct	+	-	-	-
Outcome: Lipid levels								
18	RCTs	No serious flaws	Inconsistent results between studies and between lipid parameters	Direct	-	-	-	-
2	1 nonrandomized clinical trial, 1 case-control	Limitations based on study design	Inconsistent results between studies and between lipid parameters	Direct	+	-	-	-
Outcome: Rates of progression to type 2 diabetes								
0	NA	NA	NA	NA	+	-	-	-
Outcome: Markers of carbohydrate metabolism/diabetes control								
18	RCTs	No serious flaws	Inconsistent results between head-to-head studies and placebo-controlled studies	Direct	-	-	-	-

Table 28. Quality of evidence summary table* (continued)

Studies	Design	Quality	Consistency	Directness	SD	SA	DR	PC
5	2 nonrandomized controlled trials, 1 case-control, 1 prospective observational study, 1 retrospective chart review	Limitations based on study design	Consistent results	Direct	+	-	-	-
Outcome: Measures of LV mass/function								
11	RCTs	Poor quality studies; small sample sizes	Consistent results	Direct	-	-	-	-
2	1 nonrandomized controlled trial; 1 case-control	Poor quality studies; small sample sizes	Consistent results	Direct	+	-	-	-
Outcome: Measures of kidney disease								
21 – GFR 16 – proteinuria	RCTs	Poor quality studies; different parameters measured	Consistent results Inconsistent results	Direct Direct	- -	- -	- -	- -
3 – GFR 1 – proteinuria 1 – both	1 nonrandomized controlled trial, 2 cohort studies, 1 case-control, 1 prospective observational study	Limitations based on study design	Consistent results	Direct	+	-	-	-

* Table legend:
Consistency: This column indicates whether the included studies had inconsistent results or if there is evidence of a dose response or that adjustment for confounders would have increased the effect size.
Directness: This column refers to issues that may limit the generalizability of the reported results to our specified population of interest. Such issues may include, for example, a restricted population in trials, the inclusion of too broad a population in trials, or the use of co-interventions in addition to our intervention of interest.
AEs = adverse events; DR = dose response; GFR = glomerular filtration rate; LV = left ventricular; PC = all plausible confounders would reduce the effect; RCT(s) = randomized controlled trial(s); SA = strong association (+ = very strong, ++ = extremely strong); SD= sparse data; - = no relevant data

Table 29. GRADE balance sheet

Outcome	Number of patients treated with ACEIs, ARBs, or direct renin inhibitors and assessed for outcome of interest			Effect based on meta-analysis	Quality	Relative importance
	ACEI	ARB	Direct renin inhibitor	Effect (95% CI)		
BP reduction	~ 13,600	~ 13,600	1104	-	High	Critical
Rate of use of a single antihypertensive for BP control	~12,840	~12,840	No data	Estimated odds ratio of ARBs vs. ACEIs 1.083 (95% CI 0.937 to 1.252)	High	
Mortality and major CV events	~18,700	~18,700	1104	-	Moderate	Critical
Morbidity/Quality of life	~ 550	~ 550		No difference detected	Low	-
Cough	45,441	22,437	877	Estimated odds ratio of ARBs vs. ACEIs 0.212 210 (95% CI 0.158 to 0.279) Estimated odds ratio of direct renin inhibitors vs. ACEIs 0.333 (95% CI 0.2241 to 0.4933)	High Low	
Adverse events – withdrawals	4744	4935	877	Estimated odds ratio of ARBs vs. ACEIs 0.565 (95% CI 0.453 to 0.704) Estimated odds ratio of direct renin inhibitors vs. ACEIs 0.886 (95% CI 0.458 to 1.714)	High	Critical
Persistence/ adherence	158,571	157,706	877	-	Moderate	
Lipid levels	5112	5278	No data	-	Moderate	-
Progression to type 2 diabetes	No data	No data	No data	-	Low	-
Markers of carbohydrate metabolism/diabetes control	5042	5191	No data	-	Moderate	-
Measures of LV mass/function	~777	~545	~233	-	Low	-

Table 29. GRADE balance sheet (continued)

Outcome	Number of patients treated with ACEIs, ARBs, or direct renin inhibitors and assessed for outcome of interest			Effect based on meta-analysis	Quality	Relative importance
	ACEI	ARB	Direct renin inhibitor	Effect (95% CI)		
Measures of kidney disease – creatinine/GFR	1004	483	457	Serum creatinine: Standardized mean difference of ARBs vs. ACEIs 0.109 (95% CI -0.054 to 0.272) Creatinine clearance: Standardized mean difference of ARBs vs. ACEIs -0.217 (95% CI -0.515 to 0.080) GFR: Standardized mean difference of ARBs vs. ACEIs -0.227 (95% CI -0.486 to 0.032) All flow studies: Standardized mean difference of ARBs vs. ACEIs -0.227 (95% CI -0.396 to -0.028)	Moderate	-
Measures of kidney disease – proteinuria	334	242	73	-	Low	-

BP = blood pressure; CI = confidence interval; CV = cardiovascular; GFR = glomerular filtration rate; LV = left ventricular; - = no relevant data

Future Research

With the exception of rates of cough, the hypothesis that angiotensin-converting enzyme inhibitor(s) (ACEIs), angiotensin II receptor blocker(s)/antagonist(s) (ARBs), and direct renin inhibitors have clinically meaningful differences in long-term outcomes in individuals with essential hypertension is not strongly supported by the available evidence. Given the importance of these issues, it is notable how few large, long-term, head-to-head studies have been published.

Further comparative studies in this area should emphasize:

- Subgroups of special importance such as individuals with essential hypertension and diabetes mellitus, congestive heart failure, chronic kidney disease, and dyslipidemia.
- Pragmatic designs such as clinical trials in which treatment is consistent with typical clinical practice, or randomization by organizationally meaningful clusters, such as practice organizations or health plans.
- Outcomes over several years, so that cardiovascular and cerebrovascular events can be compared between the three medication classes.
- Outcomes measured according to current clinical standards.
- Cancer-related outcomes, which are infrequently reported in the existing literature.
- Broader representation of groups such as the elderly and ethnic and racial minorities.
- Evaluation of differential effects of specific ACEIs or ARBs that are not shared by other agents within their respective medication class. (Only one direct renin inhibitor, aliskiren, is currently available.)
- Long-term comparisons of direct renin inhibitors with ACEIs and ARBs.

In addition, we think that research aimed at generating additional evidence regarding four specific areas should be prioritized. These areas include:

1. Relative persistence with drug therapy across the different classes of drugs.
   Comment: Although we report with moderate confidence that persistence with drug therapy is greater with ARB treatment than with ACEI treatment, the medication discontinuation rates varied significantly across studies. Because of the important benefit of remaining on these medications for the reduction of cardiovascular and cerebrovascular outcomes, differential medication persistence may have important health implications. In addition, medication discontinuation often requires followup visits and initiation of alternative medications and therefore has health economic ramifications as well. Future studies that more precisely estimate discontinuation rates in usual clinic settings, the additional health care utilization following discontinuation, and the conditional tolerability of an ACEI or ARB following prior intolerance to one of these agents would be valuable in understanding the consequences of differential medication discontinuation.
2. Risk of new cancer diagnoses.
   Comment: Recently, a review of ARBs found a small increased risk in new cancer diagnoses in patients treated with medications in this class.[133] This link is putatively due to the role of the AT_1 receptor in regulating cell proliferation. None of the large studies included in that review were included in the current review due to differences in the target population or in the comparator medications. None of our included studies reported cancer diagnosis or cancer death as an outcome, and our review was therefore unable to

provide any further evidence supporting or refuting this hypothesis. Future research, either in large clinical trials with long term follow up or similar observational designs should examine this important outcome further.

3. The potential to gain insight on the comparative benefits and harms of ACEIs, ARBs, and direct renin inhibitors based on findings from studies evaluating patients with other, related conditions such as congestive heart failure, ischemic heart disease, and chronic kidney disease.
   Comment: While our review is restricted to patients with essential hypertension, the agents studied here have been compared in large studies for related conditions such as congestive heart failure, ischemic heart disease, and chronic kidney disease. These systematic reviews have limited inclusion of studies to those conducted in patients with the target condition at the time of enrollment (i.e., hypertension, ischemic heart disease, congestive heart failure, or nephropathy); however, all have examined an overlapping set of efficacy and safety outcomes. As a result, important direct comparison trials are often excluded from reviews such as ours because they do not meet the target condition inclusion criteria. Such was the case of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), which was excluded from this review because no results were reported exclusively for patients with hypertension. This study provided the largest direct comparison of an ACEI versus an ARB with sufficient power to detect differences in cardiovascular events. As in our review, the ONTARGET investigators found no significant difference in any clinical efficacy outcome, but greater medication discontinuation in those treated with an ACEI or a combination of an ACEI and an ARB compared to those treated with an ARB alone. It is likely that combining studies reporting identical outcomes, but in different target populations, may yield important new information, particularly for rarer events such as cancer risk, angioedema, and mortality. Future research should consider this strategy and evaluate the extent to which results differ across target condition.
4. The incidence, timing, and clinical consequences of angioedema in patients treated with ACEIs, ARBs, or direct renin inhibitors.
   Comment: Angioedema is a well-known adverse reaction to ACEIs and ARBs; however, because of its infrequent occurrence, we lacked sufficient evidence to directly compare the incidence, timing, and clinical consequences of this reaction among patients treated with ACEIs, ARBs, or direct renin inhibitors. Others have estimated that angioedema is experienced by 1 in every 1,000 patients treated with an ACEI,[132,134] and 1 to 5 of every 10,000 of those treated with an ARB.[135,136] Furthermore, others have reported a three- to fourfold increased risk of angioedema in African-American patients treated with an ACEI compared to Caucasian patients treated with an ACEI.[131,132] Future research should utilize large databases with sufficient sample sizes to obtain more precise estimates of this rare but serious event. Assessment of study designs or analyses that could explore the impact of angioedema should be prioritized.

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Acronyms and Abbreviations

ACE	angiotensin-converting enzyme
ACEI(s)	angiotensin-converting enzyme inhibitor(s)
AHRQ	Agency for Healthcare Research and Quality
ARB(s)	angiotensin II receptor blocker(s)/antagonist(s)
AT_1	angiotensin specific receptor
CER	Comparative Effectiveness Review
CRD	Centre for Reviews and Dissemination
DBP	diastolic blood pressure
EF	ejection fraction
EPC	Evidence-based Practice Centers
ESRD	end-stage renal disease
GFR	glomerular filtration rate
HbA1c	glycated hemoglobin
HCTZ	hydrochlorothiazide
HDL	high-density lipoprotein
LDL	low-density lipoprotein
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVMI	left ventricular mass index
MeSH	Medical Subject Headings
MI	myocardial infarction
RCT	randomized controlled trial
SBP	systolic blood pressure
SD	standard deviation
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SRC	Scientific Resource Center
TC	total cholesterol
TG	triglyceride
UAE	urinary albumin excretion
USPSTF	U.S. Preventive Services Task Force

Appendix A. Exact Search Strings

Search Strategies Used for the Present (Updated) Report

MEDLINE Search—Last Run December 23, 2010

1. (losartan or valsartan or telmisartan or eprosartan or candesartan or irbesartan or olmesartan).mp.
2. losartan/
3. exp angiotensin II type 1 receptor blockers/ or exp Receptors, Angiotensin/ai [Antagonists & Inhibitors]
4. (cozaar or micardis or atacand or tevetan or avapro or benicar or diovan).mp.
5. or/1-4
6. (quinapril or perindopril or ramipril or captopril or enalapril or benazepril or trandolapril or fosinopril or moexipril or enalaprilat or cilazapril or saralasin or teprotide).mp.
7. angiotensin-converting enzyme inhibitors/ or captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ or saralasin/ or teprotide/
8. 6 or 7
9. 5 and 8
10. limit 9 to yr="2006 - current"
11. limit 10 to english language
12. exp hypertension/dt
13. 11 and 12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. Randomized Controlled Trials/
17. Random Allocation/
18. Double-Blind Method/
19. Single-Blind Method/
20. or/14-19
21. Animal/ not Human/
22. 20 not 21
23. clinical trial.pt.
24. exp Clinical Trial/
25. (clinic$ adj25 trial$).tw.
26. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
27. Placebos/
28. placebo$.tw.
29. random$.tw.
30. Research Design/
31. (latin adj square).tw.
32. or/23-31
33. 32 not 21
34. Comparative Study/
35. exp Evaluation Studies/

36. Follow-Up Studies/
37. Prospective Studies/
38. (control$ or prospectiv$ or volunteer$).tw.
39. Cross-Over Studies/
40. or/34-39
41. 40 not 21
42. 22 or 33 or 41
43. 13 and 42
44. limit 43 to abstracts
45. (aliskiren or tekturna).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
46. (renin inhibitor or renin inhibitors).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
47. renin/ai
48. or/45-47
49. 5 and 48
50. 49 and 42 and 12
51. 8 and 48
52. 51 and 42 and 12
53. 50 or 52
54. limit 53 to english language
55. 43 or 54

Embase Search—Last Run December 23, 2010

1. 'benazepril'/exp OR 'captopril'/exp OR 'enalapril'/exp OR 'enalaprilat'/exp OR 'fosinopril'/exp OR 'lisinopril'/exp OR 'moexipril'/exp OR 'perindopril'/exp OR 'quinapril'/exp OR 'ramipril'/exp OR 'trandolapril'/exp OR 'lotensin'/exp OR 'capoten'/exp OR 'vasotec'/exp OR 'monopril'/exp OR 'prinivil'/exp OR 'zestril'/exp OR 'univasc'/exp OR 'aceon'/exp OR 'accupril'/exp OR 'altace'/exp OR 'mavik'/exp OR 'angiotensin converting enzyme inhibitors'/exp AND ('candesartan'/exp AND cilexetil OR 'eprosartan'/exp OR 'irbesartan'/exp OR 'losartan'/exp OR 'olmesartan'/exp AND medoxomil OR 'telmisartan'/exp OR 'valsartan'/exp OR 'atacand'/exp OR 'teveten'/exp OR 'avapro'/exp OR 'cozaar'/exp OR 'benicar'/exp OR 'micardis'/exp OR 'diovan'/exp OR 'angiotensin ii type 1 receptor blockers'/exp) AND [2006-2010]/py
2. 'benazepril'/exp OR 'captopril'/exp OR 'enalapril'/exp OR 'enalaprilat'/exp OR 'fosinopril'/exp OR 'lisinopril'/exp OR 'moexipril'/exp OR 'perindopril'/exp OR 'quinapril'/exp OR 'ramipril'/exp OR 'trandolapril'/exp OR 'lotensin'/exp OR 'capoten'/exp OR 'vasotec'/exp OR 'monopril'/exp OR 'prinivil'/exp OR 'zestril'/exp OR 'univasc'/exp OR 'aceon'/exp OR 'accupril'/exp OR 'altace'/exp OR 'mavik'/exp OR 'angiotensin converting enzyme inhibitors'/exp AND ('aliskiren'/exp OR 'tekturna'/exp OR (direct AND 'renin'/exp AND inhibitors))
3. 'candesartan'/exp AND cilexetil OR 'eprosartan'/exp OR 'irbesartan'/exp OR 'losartan'/exp OR 'olmesartan'/exp AND medoxomil OR 'telmisartan'/exp OR 'valsartan'/exp OR 'atacand'/exp OR 'teveten'/exp OR 'avapro'/exp OR 'cozaar'/exp OR 'benicar'/exp OR 'micardis'/exp OR 'diovan'/exp OR 'angiotensin ii type 1 receptor blockers'/exp AND ('aliskiren'/exp OR 'tekturna'/exp OR (direct AND 'renin'/exp AND inhibitors))

4. #1 OR #2 OR #3
5. 'hypertension'/exp
6. #4 AND #5
7. #4 AND #5 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim AND [embase]/lim

Search Strategies Used for the Original 2007 Report

MEDLINE Search 1

Used to identify studies of (a) ACEIs vs. ARBs and (b) ARBs vs. other (non-ACEI) comparators. ACEIs vs. ARBs portion of strategy also used to search the Cochrane Central Register of Controlled Trials.

Database: Ovid MEDLINE <1966 to May Week 3 2006>
Search Strategy:
---
1 (losartan or valsartan or telmisartan or eprosartan or candesartan or irbesartan or olmesartan).mp. (7801)
2 losartan/ (3821)
3 angiotensin II type 1 receptor blockers/ (1417)
4 (cozaar or micardis or atacand or tevetan or avapro or benicar or diovan).mp. (89)
5 or/1-4 (8186)
6 (quinapril or perindopril or ramipril or captopril or enalapril or benazepril or trandolapril or fosinopril or moexipril or enalaprilat or cilazapril).mp. (20419)
7 angiotensin-converting enzyme inhibitors/ or captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ (29181)
8 6 or 7 (31620)
9 5 and 8 (2561)
10 limit 9 to yr="1989 - 2006" (2561)
11 limit 10 to humans (1570)
12 limit 11 to english language (1302)
13 exp hypertension/dt (43028)
14 12 and 13 (501)
15 randomized controlled trial.pt. (225487)
16 controlled clinical trial.pt. (73200)
17 Randomized Controlled Trials/ (45397)
18 Random Allocation/ (57318)
19 Double-Blind Method/ (88071)
20 Single-Blind Method/ (10138)
21 or/15-20 (382640)
22 Animal/ not Human/ (3011569)
23 21 not 22 (360978)
24 clinical trial.pt. (447512)

25 exp Clinical Trials/ (188054)
26 (clinic$ adj25 trial$).tw. (122637)
27 ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (84242)
28 Placebos/ (25150)
29 placebo$.tw. (97000)
30 random$.tw. (351176)
31 Research Design/ (44423)
32 (latin adj square).tw. (2271)
33 or/24-32 (817761)
34 33 not 22 (760307)
35 34 not 23 (412905)
36 Comparative Study/ (1296809)
37 exp Evaluation Studies/ (574715)
38 Follow-Up Studies/ (327165)
39 Prospective Studies/ (209742)
40 (control$ or prospectiv$ or volunteer$).tw. (1678468)
41 Cross-Over Studies/ (18169)
42 or/36-41 (3339392)
43 42 not 22 (2575440)
44 43 not (23 or 35) (2038591)
45 23 or 35 or 44 (2812474)
46 14 and 45 (421)
47 limit 46 to abstracts (383)
48 46 not 47 (38)
49 5 and 13 and 23 (812)
50 5 and 13 and 15 (577)
51 limit 50 to humans (576)
52 limit 51 to english language (547)
53 limit 52 to abstracts (526)
54 53 not 47 (355)
55 47 or 54 (738)
56 from 55 keep 1-738 (738)

MEDLINE Search 2

Used to identify studies of ACEIs vs. atenolol or amlodipine.

Database: Ovid MEDLINE <1966 to June Week 2 2006>
Search Strategy:

---

1 (losartan or valsartan or telmisartan or eprosartan or candesartan or irbesartan or olmesartan).mp. (7907)
2 losartan/ (3866)
3 angiotensin II type 1 receptor blockers/ (1495)
4 (cozaar or micardis or atacand or tevetan or avapro or benicar or diovan).mp. (89)
5 or/1-4 (8317)

6 (quinapril or perindopril or ramipril or captopril or enalapril or benazepril or trandolapril or fosinopril or moexipril or enalaprilat or cilazapril).mp. (20515)
7 angiotensin-converting enzyme inhibitors/ or captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ (29405)
8 6 or 7 (31862)
9 5 and 8 (2616)
10 limit 9 to yr="1989 - 2006" (2616)
11 limit 10 to humans (1616)
12 limit 11 to english language (1344)
13 exp hypertension/dt (43234)
14 12 and 13 (513)
15 randomized controlled trial.pt. (227233)
16 controlled clinical trial.pt. (73582)
17 Randomized Controlled Trials/ (46059)
18 Random Allocation/ (57572)
19 Double-Blind Method/ (88623)
20 Single-Blind Method/ (10243)
21 or/15-20 (385737)
22 Animal/ not Human/ (3039204)
23 21 not 22 (363780)
24 clinical trial.pt. (449329)
25 exp Clinical Trials/ (189510)
26 (clinic$ adj25 trial$).tw. (124237)
27 ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (84782)
28 Placebos/ (25242)
29 placebo$.tw. (97782)
30 random$.tw. (355789)
31 Research Design/ (44740)
32 (latin adj square).tw. (2283)
33 or/24-32 (825939)
34 33 not 22 (767683)
35 34 not 23 (417884)
36 Comparative Study/ (1313583)
37 exp Evaluation Studies/ (581443)
38 Follow-Up Studies/ (330247)
39 Prospective Studies/ (211855)
40 (control$ or prospectiv$ or volunteer$).tw. (1701806)
41 Cross-Over Studies/ (18356)
42 or/36-41 (3382854)
43 42 not 22 (2610193)
44 43 not (23 or 35) (2068318)
45 23 or 35 or 44 (2849982)
46 14 and 45 (430)
47 limit 46 to abstracts (392)
48 46 not 47 (38)
49 5 and 13 and 23 (826)

50 5 and 13 and 15 (589)
51 limit 50 to humans (588)
52 limit 51 to english language (559)
53 limit 52 to abstracts (538)
54 53 not 47 (363)
55 47 or 54 (755)
56 8 and 13 and 45 (5143)
57 amlodipine.mp. or Amlodipine/ (2102)
58 atenolol.mp. or Atenolol/ (5762)
59 57 or 58 (7736)
60 8 and 59 (1120)
61 60 and 13 (767)
62 61 and 45 (678)
63 61 and 23 (501)
64 61 and 15 (388)
65 limit 64 to humans (388)
66 limit 65 to english language (369)
67 limit 66 to abstracts (354)
68 from 67 keep 1-354 (354)

MEDLINE Search 3

Used to identify studies of ACEIs vs. placebo published after the June 2005 Drug Class Review on Angiotensin Converting Enzyme Inhibitors.*

Database: Ovid MEDLINE <1966 to June Week 4 2006>
Search Strategy:

---

1 (losartan or valsartan or telmisartan or eprosartan or candesartan or irbesartan or olmesartan).mp. (7931)
2 losartan/ (3878)
3 angiotensin II type 1 receptor blockers/ (1523)
4 (cozaar or micardis or atacand or tevetan or avapro or benicar or diovan).mp. (90)
5 or/1-4 (8352)
6 (quinapril or perindopril or ramipril or captopril or enalapril or benazepril or trandolapril or fosinopril or moexipril or enalaprilat or cilazapril).mp. (20553)
7 angiotensin-converting enzyme inhibitors/ or captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ (29480)
8 6 or 7 (31944)
9 5 and 8 (2631)
10 limit 9 to yr="1989 - 2006" (2631)
11 limit 10 to humans (1629)

* Chou R, Helfand M, Carson S. Drug Class Review on Angiotensin Converting Enzyme Inhibitors. Final Report. June 2005. Available at: www.ohsu.edu/drugeffectiveness/reports/final.cfm. Accessed 17 August 2006.

12 limit 11 to english language (1356)
13 exp hypertension/dt (43305)
14 12 and 13 (516)
15 randomized controlled trial.pt. (227810)
16 controlled clinical trial.pt. (73653)
17 Randomized Controlled Trials/ (46324)
18 Random Allocation/ (57680)
19 Double-Blind Method/ (88793)
20 Single-Blind Method/ (10281)
21 or/15-20 (386780)
22 Animal/ not Human/ (3043394)
23 21 not 22 (364697)
24 clinical trial.pt. (449647)
25 exp Clinical Trials/ (190053)
26 (clinic$ adj25 trial$).tw. (124749)
27 ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (84961)
28 Placebos/ (25278)
29 placebo$.tw. (98008)
30 random$.tw. (356966)
31 Research Design/ (44861)
32 (latin adj square).tw. (2289)
33 or/24-32 (828165)
34 33 not 22 (769721)
35 34 not 23 (419156)
36 Comparative Study/ (1316751)
37 exp Evaluation Studies/ (582995)
38 Follow-Up Studies/ (331073)
39 Prospective Studies/ (212521)
40 (control$ or prospectiv$ or volunteer$).tw. (1706292)
41 Cross-Over Studies/ (18430)
42 or/36-41 (3391311)
43 42 not 22 (2617037)
44 43 not (23 or 35) (2073600)
45 23 or 35 or 44 (2857453)
46 14 and 45 (432)
47 limit 46 to abstracts (393)
48 46 not 47 (39)
49 5 and 13 and 23 (829)
50 5 and 13 and 15 (590)
51 limit 50 to humans (589)
52 limit 51 to english language (560)
53 limit 52 to abstracts (539)
54 53 not 47 (364)
55 47 or 54 (757)
56 8 and 13 and 45 (5155)
57 amlodipine.mp. or Amlodipine/ (2108)

58 atenolol.mp. or Atenolol/ (5772)
59 57 or 58 (7752)
60 8 and 59 (1123)
61 60 and 13 (768)
62 61 and 45 (679)
63 61 and 23 (502)
64 61 and 15 (389)
65 limit 64 to humans (389)
66 limit 65 to english language (370)
67 limit 66 to abstracts (355)
68 from 67 keep 1-354 (354)
69 56 and (28 or 29) (1286)
70 limit 69 to humans (1286)
71 limit 70 to english language (1154)
72 limit 71 to abstracts (1150)
73 (2005$ or 2006$).ed. (974282)
74 72 and 73 (52)
75 from 74 keep 1-52 (52)

Appendix B. Methods for Reviewing Indirect Comparison Studies

Introduction

Our original 2007 review of the literature on the comparative long-term benefits and harms of angiotensin-converting enzyme inhibitors (ACEIs) versus angiotensin II receptor antagonists (ARBs) for treating hypertension focused, in the first instance, on direct head-to-head comparisons of drugs in the two classes. In that report, because we were uncertain that these direct comparisons would adequately address all aspects of the key questions, we also sought to identify and screen potentially relevant indirect comparison studies—that is, studies in which ACEIs and ARBs were compared, in distinct trials, with a common comparator. This appendix describes the methods we used to identify and review indirect comparison studies as part of the original report. Given the findings of that analysis—and subsequent decision to restrict our updated report to direct head-to-head comparisons—we did not repeat this analysis using the updated evidence base.

Search and Abstract Screening

We began by searching MEDLINE for studies of ARBs versus other (non-ACEI) comparators, including placebo (see MEDLINE Search 1 in Appendix A). We screened these abstracts along with the head-to-head trials (see the abstract screening criteria in Appendix C). Note that, for indirect comparisons, we considered only randomized controlled trials (RCTs). We coded each included abstract for treatment duration/length of followup ("12 weeks", "1 year", etc.).

Because a primary objective for evaluating non-head-to-head studies was to expand the pool of evidence regarding long-term results, we restricted the pool of abstracts for further evaluation to those with a treatment duration/length of followup of ≥ 24 weeks. Further, since the credibility of any meta-analysis – particularly for non-head-to-head trials – depends on consistency among studies, we considered only comparators for which there were ≥ 3 trials. The comparators thus identified were atenolol, amlodipine, and placebo.

Next, we searched MEDLINE for studies of ACEIs versus atenolol or amlodipine (see MEDLINE Search 2 in Appendix A). To identify potentially relevant ACEI-versus-placebo trials, we began by searching the references of the June 2005 Drug Class Review on Angiotensin Converting Enzyme Inhibitors[*] and supplemented this with a search of MEDLINE for articles published after that review (see MEDLINE Search 3 in Appendix A). Finally, the abstracts for all ACEI-versus-other studies were screened for inclusion and evaluated further to identify trials with the right treatment duration/length of followup (≥ 24 weeks) and the right comparators (atenolol, amlodipine, or placebo).

The result of this process was that we identified 76 RCT publications comparing ARBs with atenolol, amlodipine, or placebo over a period of ≥ 24 weeks, and 136 RCT publications comparing ACEIs with the same group of comparators over the same period of time. We were

[*] Chou R, Helfand M, Carson S. Drug Class Review on Angiotensin Converting Enzyme Inhibitors. Final Report. June 2005. Available at: www.ohsu.edu/drugeffectiveness/reports/final.cfm. Accessed 17 August 2006.

unable to obtain copies of 4 articles (2 each for ACEIs and ARBs), so the final counts were 74 potentially relevant ARB articles and 134 potentially relevant ACEI articles.

Identifying Publications Reporting Outcomes of Interest

Once data from the direct comparator trials had been abstracted, we identified three categories of outcomes that we thought were under-reported in these trials:

- Mortality and major events (myocardial infarction [MI], stroke);
- Measures of carbohydrate metabolism/diabetes control (progression to type 2 diabetes, glycated hemoglobin [HgbA1c], insulin or other diabetes medication dosage, fasting plasma glucose, or aggregated measures of serial glucose measurements);
- Measures of kidney disease (creatinine/glomerular filtration rate [GFR] and proteinuria).

We then screened the indirect comparison literature identified through the process described above in full-text form to identify publications that reported on one or more of these outcomes. Thirty-two (32) ARB-versus-other publications and 42 ACEI-versus-other publications reported one or more of the outcomes of interest and were evaluated further. A list of these 74 publications is provided at the end of this Appendix.

Analysis of Comparability of Trials

In consideration of the special challenges of using indirect (non-head-to-head) comparison studies to infer relative efficacy regarding any particular health outcome, we established minimal criteria before considering any indirect comparison. Our goal was to achieve a reasonable degree of clinical homogeneity without being excessively restrictive at this stage.

We defined three criteria for considering performing an indirect comparison. The first criterion was that the studies must have a common comparator (amlodipine, atenolol, or placebo). The rationale is that comparators cannot be considered equivalent with regard to any particular health outcome. The second criterion was that study populations must be generally comparable, at least with regard to key characteristics relevant to the outcome being assessed. For studies examining event rates (mortality, stroke, or MI), the key characteristic was the mean age of the population. For studies of laboratory measures (HgbA1c, glucose, creatinine, GFR, or proteinuria), the key characteristic was the mean of the corresponding laboratory measure at baseline. The value for the key characteristic could be different by as much as 10 percent and still be considered to be comparable (e.g., for mortality rates in which the study with the highest mean age for subjects was 70 years, comparable studies could have mean subject ages as low as 63 years). The third criterion was that among studies satisfying the preceding criteria, there must be more than one study of an ACEI versus the comparator and more than one study of an ARB versus the comparator. That is, indirect comparisons for a particular outcome would be considered only if there were at least four comparable studies to evaluate, two for an ACEI and two for an ARB. Notably, we did not restrict studies to the same ACEI or ARB, or any other protocol characteristics.

Despite these relatively liberal criteria for considering indirect comparisons between ACEIs and ARBs, we did not identify any appropriate candidate studies related to an outcome of special interest, and thus we did not attempt to use indirect evidence to infer relative impact of ACEIs versus ARBs.

List of Indirect Comparator Articles Reaching the Final Stage of Evaluation

The following is a list of the 74 indirect comparator publications from our original report that met our basic screening criteria (RCT, followup ≥ 24 weeks, comparator with ≥ 3 trials on ACEI and ARB sides) and reported one or more of the outcomes of interest specified above (mortality, MI, stroke, diabetes outcomes, kidney disease outcomes).

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Appendix C. Abstract and Full-Text Screening Criteria

Abstract Screening Criteria

An abstract will be **included** if all of the following criteria apply:

- The study is a direct comparison (any study design) of an angiotensin-converting enzyme inhibitor (ACEI) versus an angiotensin II receptor antagonist (ARB), or an ACEI versus a renin inhibitor, or an ARB versus a renin inhibitor (see lists at end of this document for included drugs; additional antihypertensive therapy OK if the same in both groups);
- Original data.

An abstract will be **excluded** if any of the following criteria apply**:**

- No patients have hypertension OR some patients have hypertension, but results not reported separately for this subgroup;
- All subjects aged < 18 years OR some subjects aged < 18 years, but results not broken down by age;
- Only comparison is an ACEI + an ARB versus placebo.

An abstract will be identified as a **review** if it is a relevant review article, meta-analysis, methods article, or cost-effectiveness analysis.

For each abstract, please mark either **"EX"** for **Exclude, "IN"** for **Include** or **"Rev"** for **Review.**

For included studies, please mark:

- **"AcVAr"** if the study is a **direct comparison** of an ACEI versus an ARB;
- **"AcVR"** if the study is a **direct comparison** of an ACEI versus a direct renin inhibitor
- **"ArVR"** if the study is a **direct comparison** of an ARB versus a direct renin inhibitor

For all included studies, please also indicate the longest length (weeks or months) of followup.

Thus, coding for each abstract should be either:

- EX
- Rev
- IN AcVAr (specify # weeks or # months followup, or write "NS" if length of followup not specified)
- IN AcVR (specify # weeks or # months followup, or write "NS" if length of followup not specified)
- IN ArVR (specify # weeks or # months followup, or write "NS" if length of followup not specified)
- Info (if full-text needed to assess eligibility)

Full-Text Screening Criteria

Note: Screeners were instructed to work from top to bottom of the following list, choosing the first (if any) exclusion reason that applied.

1. Condition of interest = essential hypertension
   - ***Exclude*** if no patients have essential hypertension *or* if results not reported separately for subgroup with essential hypertension
2. Population of interest = adults (≥ 18 years)
   - *Exclude* if all subjects < 18 *or* if results not reported separately for ≥ 18 subgroup
3. Interventions & comparators of interest:
   <u>ACEIs, ARBs, and direct renin inhibitors listed at end of this document</u>
   - ***Include*** "grouped" comparisons, e.g., specific ARB vs. "ACE inhibitors" or unspecified "ARBs" vs. unspecified "ACEIs"
   - ***Include*** ACEI + drug X vs. ARB + drug X (e.g., losartan + HCTZ vs. enalapril + HCTZ)
   - ***Exclude*** ACEI + drug X vs. ARB + drug Y (e.g., enalapril + manidipine vs. irbesartan + HCTZ)
   - ***Exclude*** if ACEI , ARB, or direct renin inhibitor not on lists at end of this document
4. Study designs:
   - ***Include*** all clinical study designs (RCTs, non-RCTs, cohorts, etc.); cross-sectional studies OK if time on treatment reported and ≥ 12 weeks
   - ***Exclude*** if not clinical study (review, etc. – please specify)
5. Outcomes of interest:
   For Key Question 1 and 3:
   - Intermediate outcomes:
     - Blood pressure control
     - Rate of use of a single antihypertensive agent for blood pressure control
     - Lipid levels
     - Progression to type 2 diabetes
     - Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], dosage of insulin or other diabetes medication, fasting plasma glucose, aggregated measures of serial glucose measurements)
     - LV mass/function
     - Creatinine/GFR
     - Proteinuria
   - Health outcomes:
     - Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific)
     - Morbidity (cardiac events (myocardial infarction, heart failure, cerebral vascular disease or events [including stroke], symptomatic coronary artery disease, end-stage renal disease, PVD [as clinically manifest, not markers of], quality of life)

   For Key Question 2 and 3:
   - Safety (overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, switch rates)
   - Specific adverse events (including, but not limited to: weight gain, impaired renal function, angioedema, cough, hyperkalemia)
   - Tolerability
   - Persistence

- Adherence

6. Sample size:
   - We will not exclude articles based on sample size during the full text screening but may re-visit this decision when performing the full-text abstraction and synthesis.
7. Treatment duration/length of followup:
   - ***Exclude*** if treatment duration or longest followup < 12 weeks

Included ACEIs

Benazepril (Lotensin)
Captopril (Capoten)
Enalapril/Enalaprilat (Vasotec; Enalaprilat IV)
Fosinopril (Monopril)
Lisinopril (Prinivil, Zestril)
Moexipril (Univasc)
Perindopril (Aceon)
Quinapril (Accupril)
Ramipril (Altace)
Trandolapril (Mavik)

Included ARBs

Candesartan cilexetil (Atacand)
Eprosartan (Teveten)
Irbesartan (Avapro)
Losartan (Cozaar)
Olmesartan medoxomil (Benicar)
Telmisartan (Micardis)
Valsartan (Diovan)

Included direct renin inhibitor

Aliskiren (Tekturna)

Appendix D. Data Abstraction Form

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
StudyID	Geographical location: [city & state (U.S.) or city & country (foreign)] Study dates: [month & year] Funding source: Interventions: [For each treatment arm, describe drug, dose (incl. titration protocol), and number of patients randomized] Were additional anti-hypertension medications allowed: [Delete all but one] Yes/No/ NR = not reported If Yes to above, was this done: [delete all but one] Per protocol At discretion of clinician/investigator NR Study design: [Delete all but one] RCT, parallel-group RCT, crossover Other [specify]	Number of patients: - Screened for inclusion: - Eligible for inclusion: - Randomized: - Began treatment: - Completed treatment: - Withdrawals/losses to followup: Age: Mean (SD): Median: Range: **Sex (n [%]):** Female: Male: Race/ethnicity (n [%]): **Baseline blood pressure:** [by treatment group, if given; indicate how assessed] **Concurrent non-hypertension medications (n [%]):** **Comorbidities (n [%]):** **Recruitment setting:** [Inclusion/exclusion criteria: describe these as reported in article. If tolerability was	[Where necessary, specify how outcomes were defined and assessed. Report quantitative data and p-values, where available; give N's for specific outcomes if these differ from N's randomized; give time point(s) for abstracted data and note other time points available in the article. Include any results reported separately for subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or co-morbidities.] **1) Blood pressure:** [Prefer seated trough BP, if reported; if BP outcomes other than the one(s) you abstract are reported, list these] **2) Rate of use of a single antihypertensive agent for BP control:** **3) Mortality:** [all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific] **4) Morbidity:** [cardiac events (MI), heart failure, cerebral vascular disease or events (incl. stroke), symptomatic coronary artery disease, end-stage renal disease, PVD, quality of life] **5) Safety:** [overall adverse events (AEs), withdrawals	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] **General comments:** [Comment here on biases, etc., affecting clinical interpretation] Quality assessment: [Assign an overall quality rating of "Good," "Fair," or "Poor" based on the definitions provided in the guidance sheet. If study is rated as "Fair" or "Poor," note important limitations in internal validity (see guidance sheet assessing quality) under "Comments", below.] Overall rating: Comments: **Applicability:** [List the most important (up to 3) limitations affecting applicability, if any, based on the list given in the guidance sheet on assessing applicability.] **This article is relevant to:** [Delete as appropriate] Question 1 Question 2 Question 3

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		assessed during run-in or used as an incl/excl criterion, please note this.]	due to AEs, serious AEs reported, switch rates]	
	Blinding: [For each item, Yes/No/NR] - Patients: - Providers: - Assessors of outcomes:	Inclusion criteria:	**6) Specific adverse events:** [including, but not limited to: weight gain, impaired renal function, hyperkalemia, angioedema, cough]:	
	Was allocation concealment adequate? [e.g., computer-generated list or central randomization] Yes/No/NR	Exclusion criteria:	**7) Persistence/adherence:**	
	Baseline/run-in period: [length & intervention, or NA = not applicable]		**8) Lipid levels:**	
			9) Progression to type 2 diabetes:	
	Washout period(s): [crossover trials only; length]		**10) Markers of carbohydrate metabolism/diabetes control:** [HbA1c, insulin or other diabetes med dosage, fasting plasma glucose, aggregated measures of serial glucose measurements]	
	Duration of treatment: [post-baseline/run-in; days, weeks, months]			
	Duration of post-treatment followup: [days, weeks, months, or NA = not applicable]		**11) LV mass/function:**	
			12) Creatinine/GFR:	
			13) Proteinuria:	

Appendix E. Evidence Table

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Akat, Bapat, Murthy, et al., 2010 **#2132**	Geographic location: Miraj, India Study dates: NR Funding source: None Interventions: 1) Telmisartan 40 mg/d 2) Enalapril 10 mg/d Were additional anti-hypertension medications allowed: NR If Yes to above, was this done: NR Study design: RCT, parallel-group Blinding: - Patients: NR - Providers: NR - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: 4 wks of voluntary discontinuation of anti-HTN meds prior to start of study Washout period(s): NA Duration of treatment: 12 weeks Duration of post-treatment followup: NA	Number of patients: N = 80 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 80 - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR Age: Mean (SD): NR Median: NR Range: 18-65 **Sex (n [%]):** Female: NR Male: NR Race/ethnicity (n [%]): NR **Baseline blood pressure:** BP recorded in a sitting position after 10 minutes of rest Baseline SBP: Telmisartan: 154.72 ± 12.52 Enalapril: 156.05 ± 10.56 Baseline DBP: Telmisartan: 98.22 ± 3.78 Enalapril: 98.34 ± 4.45 **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR	**1) Blood pressure:** <u>SBP</u> Baseline: Telmisartan: 154.72 ± 12.52 Enalapril: 156.05 ± 10.56 2 weeks: Telmisartan: 143.16 ± 10.33 Enalapril: 141.6 ± 17.94 4 weeks: Telmisartan: 138.94 ± 9.47 Enalapril: 139.82 ± 9.37 8 weeks: Telmisartan: 133.61 ± 8.29 Enalapril: 133.77 ± 8.53 12 weeks: Telmisartan: 128.33 ± 7.50 Enalapril: 129.31 ± 7.32 <u>DBP</u> Baseline: Telmisartan: 98.22 ± 3.78 Enalapril: 98.34 ± 4.45 2 weeks: Telmisartan: 90.05 ± 1.47 Enalapril: 90.62 ± 1.66 4 weeks: Telmisartan: 88.94 ± 2.36 Enalapril: 89.77 ± 1.26 8 weeks: Telmisartan: 86.44 ± 3.61 Enalapril: 89.37 ± 2.04	**General comments:** None Quality assessment: Overall rating: Poor Comments: - Inadequate reporting of patient recruitment, screening, selection, and retention - Inadequate reporting of co-interventions - Statistical analyses not entirely appropriate **Applicability:** - Inadequate description of patient population and clinical settings - Conducted in India - No information about co-interventions

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Inclusion criteria: - Mild to moderate essential hypertension - Either sex Age 18-65 years - Either newly diagnosed or had discontinued antihypertensive medication voluntarily for more than 4 weeks Exclusion criteria: - On other antihypertensive therapy - Secondary hypertension - Impaired liver function (defined as SGOT or SGPT > 2 times normal limit) - History suggestive of obstructive biliary disease, cholestasis or severe hepatic impairment - Female, of child-bearing age, and not using medically approved contraceptives	12 weeks: Telmisartan: 84.22 ± 3.78 Enalapril: 88.63 ± 1.35 **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** Fatigue Telmisartan: 2.77% Enalapril: 2.85% Headache Telmisartan: 2.77% Enalapril: 2.85% Dizziness Telmisartan: 2.77% Enalapril: 2.85% Cough Telmisartan: 0% Enalapril: 11.43% ($p < 0.05$) **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			11) LV mass/function: NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Amerena, Pappas, Ouellet, et al., 2002 **#1555**	Geographical location: Multi-national, multicenter: Canada (14 sites), Australia (12), Germany (11), Italy (9), Greece (7), Russia (6), Spain (5), Hungary (5), Czech Republic (4), Lithuania (2) Study dates: NR Funding source: NR (one author affiliated with GSK) Interventions: - Telmisartan (40-80 mg) (n = 264) - Enalapril (10-20 mg) (n = 258) Titrated to higher dose if mean DBP > 90 at wk 6 Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: Yes for most outcomes except mean seated trough DBP Was allocation concealment adequate?: NR Baseline/run-in period: 4 wk placebo	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: 882 - Randomized: 522 - Began treatment: 522 - Completed treatment: 482 - Withdrawals/losses to followup: 40 patients prematurely discontinued treatment (12 due to AEs, reasons for others NR) and 6 more were excluded from ITT analysis (no on-therapy efficacy data) - ITT population: 516 (522-6 patients with no efficacy data) Age: Mean (SD): 52 ± 9.6 Median: NR Range: 23 - 77 **Sex (n [%]):** Female: 184 (36%) Male: 332 (64%) Race/ethnicity (n [%]): White: 503 (97%) Asian + other: 13 (3%) **Baseline blood pressure:** Seated unblinded trough (24 hr post-dose) SBP and DBP measured using an automated ABPM SpaceLabs 90207 device; mean of 3 measurements used	**1) Blood pressure:** Change from baseline in mean seated trough BP values at 12 wk (mean values NR): Telmisartan (n = 250); Enalapril (n = 247); p SBP:-11.90; -10.42; p = ns DBP:-9.69; -7.67; p < 0.02 DBP response at 12 wk (seated trough DBP < 90 mm Hg and/or a ≥ 10 mm Hg reduction from baseline): Telmisartan: 59% Enalapril: 50% p < 0.05 Also reported 18-24 hr and 24 hr ABPM, daytime, and nighttime BP **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Any AE: Telmisartan: 76/265 (28.7%) Enalapril: 82/257 (31.9%) AE considered to be drug-related:	**General comments:** - Patients were withdrawn from the study if DBP > 114 or their seated SBP > 200 mmHg at any time Quality assessment: Overall rating: Fair Comments: - Statistically significant endpoint not blinded **Applicability:** - No comorbidities discussed - No clear idea of recruitment strategy - Run in period on placebo may be selective to patients that got in - No real baseline information on the patients' other medical issues

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Telmisartan: 20 (7.5%)	
	Duration of treatment: 12 wk	Baseline values:	Enalapril: 34 (13.2%)	
		Telmisartan Enalapril		
	Duration of post-treatment followup: NA	SBP:159.9 ± 12.4 157.7 ± 13.2	6 serious AEs (treatment group NR), none considered to be drug-related	
		DBP:103.0 ± 6.3 101.6 ± 6.1		
		Concurrent medications (n [%]):	Discontinuation due to AEs:	
		No other antihypertensives	Telmisartan: 4 (1.5%)	
			Enalapril: 8 (3.1%)	
		Comorbidities (n [%]):	**6) Specific adverse events:**	
		NR		
			Telmisartan Enalapril	
		Recruitment setting:	(n = 265) (n = 257)	
		NR	HA22 (8.3%) 18 (7.0%)	
			Cough	
		Inclusion criteria:	2 (0.8) 23 (8.9)	
		- Age > 18	Musculoskel pain	
		- Mild to moderate essential	12 (4.5) 8 (3.1)	
		HTN, 95 ≤ DBP ≤ 114 (or 104 in	Malaise/fatigue	
		German and Czech sites)	6 (2.3) 9 (3.5)	
			Hypotension	
		Exclusion criteria:	3 (1.1) 10 (3.9)	
		- Mean SBP ≥ 180	Viral ENT infect	
		- Secondary HTN	8 (3) 7 (2.7)	
		- Uncorrected volume or sodium depletion	**7) Persistence/adherence:**	
		- Severe renal impairment, renal artery stenosis, hepatic impairment, biliary obstructive disorders, electrolyte disturbances, primary aldosteronism, or hereditary fructose intolerance	Compliance assessed by pill count at clinic visit; similar in both groups	
			8) Lipid levels: NR	
			9) Progression to type 2 diabetes: NR	
		- Known sensitivity to any component of the placebo, telmisartan, or enalapril tablets	**10) Markers of carbohydrate metabolism/diabetes control:** NR	
		- Pregnant women, breast-feeding, or women of childbearing potential not using a	**11) LV mass/function:** NR	
			12) Creatinine/GFR: NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		approved form of birth control	**13) Proteinuria:** NR	
Andersen, Weinberger, Egan, et al., 2008 **#130** **AND** **Andersen, Weinberger, Constance, et al., 2009** **#1139** **AND** **Andersen, Weinberger, Egan, et al., 2010** **#2213**	Geographical location: 92 study centers in Belgium, Canada, Hong Kong, Denmark, Iceland, Slovakia, South Africa, Spain, and USA Study dates: 26 weeks long (no dates given) Funding source: Novartis Pharma AG Interventions: Once daily treatment with: - Aliskiren (420 patients) 150 mg or - Ramipril 5mg (422 patients) Up-titration to aliskiren 300 mg or ramipril 10 mg and subsequent addition of HCTZ 12.5 mg and 25 mg were permitted sequentially for patients not achieving adequate BP control at weeks 6, 12, 18, and 21. After 26-week active treatment period, patients were re-randomized equally to either their current regimen or placebo for 4-week withdrawal period. Were additional anti-hypertension medications allowed: No (except HCTZ, as specified above)	Number of patients: N = 842 - Screened for inclusion: NR - Eligible for inclusion: 1082 - Randomized: 842 - Began treatment: 842 - Completed treatment: 675 - Withdrawals/losses to followup: 150 Age: Mean (SD): 53.3 ± 11 ≥ 65 years: 127 (15%) **Sex (n [%]):** Female: 362 (43%) Male: 480 (57%) Race/ethnicity (n [%]): White: 638 (75.8%) Black: 151 (17.9%) Asian: 27 (3.2%) Other: 26 (3.1%) **Baseline blood pressure:** Aliskiren: Mean sitting SBP: 151.3 ± 11.7 Mean sitting DBP 98.8 ± 3.4 Ramipril: Mean sitting SBP 151.5 ± 11.7 Mean sitting DBP 98.9 ± 3.5 **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** Obese:	**1) Blood pressure:** Aliskiren lowered mean sitting (ms) SBP/ms DBP to 133.7/85.8 mmHg at week 26 endpoint Ramipril lowered ms SBP/ms DBP to 136.4/87.2 mmHg Mean reductions in ms SBP and ms DBP were significantly greater with aliskiren-based therapy. Proportion of patients who had their ms SBP controlled to < 140 mmHg was significantly higher with aliskiren-based therapy (72.5%) than ramipril (64.1%) at week 26 endpoint. The proportion of patients achieving BP < 140/90 mmHg was also significantly higher with aliskiren 61.4% than with ramipril 53.1% Controlled ms SBP < 140 mmHg: 76.8% aliskeren vs. 69.9% ramipril Post hoc analyses for the subgroups of patients with metabolic syndrome, obesity, or diabetes showed that the mean decreases in ms SBP and ms DBP with both aliskiren and ramipril-based therapy were generally similar to those observed in the overall population – though BP reductions with ramipril therapy were slightly larger in the diabetes subgroup than the overall population.	**General comments:** None Quality assessment: Overall rating: Good Comments: None **Applicability:** - Not enough information about the centers where the studies were performed

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: NR Baseline/run-in period: 4 weeks placebo run-in Washout period(s): 2 weeks Duration of treatment: 26 weeks Duration of post-treatment followup: 4-week withdrawal period	Aliskiren = 184 (43.8%) Ramipril = 221 (55.4%) Metabolic syndrome: Aliskiren = 171 (40.7%) Ramipril = 183 (43.4%) Diabetes: Aliskiren = 42 (10%) Ramipril = 49 (11.8%) **Recruitment setting:** NR Inclusion criteria: - Aged ≥ 18 years - Hypertension (mean sitting DBP ≥ 90 mmHg and < 110 mmHg) Exclusion criteria: - Severe HTN (mean sitting DBP ≥ 110 mmHg or mean sitting SBP ≥ 180 mmHg) - History or evidence of secondary HTN - Known Keith-Wagener grade III or IV hypertensive retinopathy - Type 1 or type 2 DM with fasting glycosylated hemoglobin (HbA_{1c}) > 9% at screening - History of severe cerebrovascular or cardiovascular disease - Any condition that may alter the absorption, distribution, metabolism, or excretion of study drugs - Pregnant or nursing women	Post hoc analysis for the subgroup of patients with stage 2 HTN who completed the 12-week monotherapy phase (n = 88 for aliskiren, n = 87 for ramipril) demonstrated a reduction in SBP and DBP of 22.3 and 12.7 mm Hg, respectively, with aliskiren, and a reduction in SBP and DBP of 18.1/10.2 mm Hg, respectively, with ramipril at 12 weeks. Among this subgroup of patients, aliskiren was non-inferior (p < 0.0001) to ramipril for SBP reduction with non-significant superiority (p = 0.052), and superior (p = 0.043) to ramipril for DBP reduction. **2) Rate of use of a single antihypertensive agent for BP control:** Aliskeren: 220/420 (52%) Ramipril: 209/422 (49.5%) Subgroup of patients who received only monotherapy during 26-week treatment period (ITT population aliskiren n = 220, ramipril n = 209): Aliskiren ms SBP/ms DBP 149.8/98.4 to 132.8/85.1 mmHg; ramipril 148.7/98.5 to 135.8/87 mmHg **3) Mortality:** One patient died due to mesenteric thrombosis 6 days after discontinuing treatment with ramipril 10 mg plus HCTZ 25mg; the death was not considered related to study medication. **4) Morbidity:** NR **5) Safety:** | | Aliskiren | Ramipril | | Any AE | 257 | 255 |	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	(61.3%)	(60.4%)
Any serious AE	8 (1.9)	6 (1.4)
Discontinu-ation due to AE	24 (5.7%)	20 (4.7%)

6) Specific adverse events:
Cough reported more than twice as frequently by patients receiving ramipril (9.5%) than aliskiren (4.1%)

Cough judged to be treatment-related (ramipril 5.5%, aliskiren 2.1%)

Headache more common with aliskiren than ramipril (11.2 vs. 8.3%) but rates of treatment-related headache were low and similar in the two groups (aliskiren 1.4%, ramipril 1.7%)

Discontinuation due to cough was more common with ramipril 2.1% than aliskiren 1.0%

Only one serious adverse event was considered related to study medications, namely, a case of angioneurotic edema in one patient receiving aliskiren 150 mg, who recovered completely following discontinuation of study medication

	Aliskiren	Ramipril
Headache	47 (11.2)	35 (8.3)
Naso-pharyngitis	25 (6)	26 (6.2)
Dizziness	23 (5.5)	20 (4.7)
Fatigue	18 (4.3)	15 (3.6)
Cough	17 (4.1)	40 (9.5)
Diarrhea	16 (3.8)	7 (1.7)

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Peripheral edema	16 (3.8)	13 (3.1)
Back pain	15 (3.6)	13 (3.1)
Pain in extremity	15 (3.6)	8 (1.9)
Bronchitis	13 (3.1)	4 (0.9)
URTI	12 (2.9)	17 (4.0)
Nausea	11 (2.6)	8 (1.9)
Dyspepsia	10 (2.4)	4 (0.9)
Sinusitis	8 (1.9)	10 (2.4)
Influenza	8 (1.4)	11 (2.6)

7) Persistence/adherence:
Aliskiren: 79 (18.8%) discontinued
Ramipril: 72 (16.8%) discontinued

8) Lipid levels: NR

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: NR

11) LV mass/function: NR

12) Creatinine/GFR:

	Aliskiren	Ramipril
Potassium < 3.5 mmol/L	22 (5.3)	19 (4.6)
Potassium > 5.5 mmol/L	8 (1.9)	4 (1.0)
Potassium ≥ 6□0 mmol/L	2 (0.5)	1 (0.9)
BUN > 14.28 mmol/L	1 (0.2)	1 (0.2)

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results			Comments/ quality/applicability
			Creatinine > 176.8 umol/L	0	3 (0.7)	
			13) Proteinuria: NR			
Avanza, El Aouar, and Mill, 2000 **#1559**	Geographical location: Vitoria, Brazil Study dates: Unknown Funding source: Merck Sharp & Dhome – supplied meds Interventions: - Enalapril 20 mg qam + 15 mg qpm (n = 22) - Losartan 100 mg qam + 75 mg qpm (n = 17) - Enalapril 15 mg qam + losartan 100 mg qpm (n = 23) No dose titration; no co-interventions permitted Study design: Non-randomized controlled clinical trial (CCT) Groups assigned sequentially as patients were recruited: Enalapril → enalapril/losartan → losartan Blinding: - Patients: No - Providers: No - Assessors of outcomes: Yes (echocardiographers were blinded)	Number of patients: - Screened for inclusion: 90 - Eligible for inclusion: 61 - Allocated: 61 - Began treatment: 61 - Completed treatment: 46 - Withdrawals/losses to followup: 15 (4 due to cough, 4 stopped taking study med, 2 noncompliant, 2 altered medication schedule, 2 treatment failures, 1 acute MI) Age: Mean (SD): 54 ± 4 **Sex (n [%]):** Female: 19 (41%) Male: 27 (59%) Race/ethnicity (n [%]): "All were white or mulatto" (no numbers given) **Baseline blood pressure:** Office BP measured using a mercury sphygmomanometer after a 10-min rest in a seated position: Mean baseline values for n = 46 study completers: <u>SBP</u> <u>DBP</u>	**1) Blood pressure:** Mean office SBP values reported in text for 7 mo. Posttreatment office DBP for all timepoints and office SBP for all other timepoints reported only graphically in Figure 1. Mean office SBP at 7 mo: Enalapril (n = 15): 146 ± 1.9 Losartan (n = 15): 146 ± 2.1 Enalapril + losartan (n = 16): 143 ± 1.9 p > 0.05 for between-group comparison of reductions from baseline At 10 mo, SBP values significantly (p < 0.05) higher in the losartan group than in the other 2 groups (shown only graphically in Figure 1) At the end of month 10 "almost all the patients" had BPs in the normal range (SBP < 140 mm Hg, DBP < 90 mm Hg) **2) Rate of use of a single antihypertensive agent for BP control:** NA (no other antihypertensives permitted) **3) Mortality:** NR **4) Morbidity:** 1 patient in the enalapril group had an acute MI **5) Safety:**		**General comments:** None Quality assessment: Overall rating: Poor Comments: - Poor study design - Non-randomized, non-blinded - Small sample size - Non-responders and non-compliant patients excluded from analysis - Reported levels of SBP reduction are far greater than that typically reported in most studies - Missing data, including BP values at 10 months **Applicability:** - Minimal patient characteristics reported - Black patients excluded - Analyzed very selected population who completed study, complied with treatment, and responded to treatment (not ITT)

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Enalapril 173 ± 2.9 104 ± 1.8	4/22 patients (18%) in the enalapril group withdrew due to cough	
	Was allocation concealment adequate?: No	Losartan 170 ± 1.9 103 ± 1.7	**6) Specific adverse events:** NR	
	Baseline/run-in period: 12-day washout of prior meds	Enalapril + losartan 173 ± 2.8 104 ± 1.5	**7) Persistence/adherence:** 2/61 patients were noncompliant (both enalapril)	
	Duration of treatment: 10 months		4/61 stopped taking study medication (2 losartan, 2 combination group)	
	Duration of post-treatment followup: NA	24-hr ABPM also performed using a SpaceLabs 90207 device, with readings every 20 min	2/61 altered medication schedule (both combination group)	
		Concurrent medications (n [%]): NR	**8) Lipid levels:** NR	
			9) Progression to type 2 diabetes: NR	
		Comorbidities (n [%]): NR	**10) Markers of carbohydrate metabolism/diabetes control:**	
		Recruitment setting: University clinics	Plasma glucose levels (mg%) were in the normal range for all patients and did not change significantly during treatment. There were no significant between-group differences.	
		Inclusion criteria: - Both sexes - Age 40-60 - Resting BP indicating moderate hypertension (by JNC-5) after run-in - Ambulatory BP confirming moderate hypertension - Echo criteria for LVH	<u>Baseline</u> <u>10 mo</u> Enalapril (n = 15) 90 ± 4 90 ± 4 Losartan (n = 15) 93 ± 4 94 ± 4 Enalapril + losartan (n = 16) 91 ± 4 91 ± 4	
		Exclusion criteria: - Black race - Obesity (BMI >30) - Diabetes - Valvular heart disease - Secondary hypertension - History of complications of hypertension (MI or CHF)	**11) LV mass/function:** Mean LVMI (g/m^2) <u>Baseline</u> <u>10 mo</u> Enalapril (n = 15) 141 ± 3.9 123 ± 3.6 Losartan (n = 15)	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Long-term use of corticosteroids, neuroleptics or antidepressants	147 ± 3.8 133 ± 2.8 Enalapril + losartan (n = 16) 146 ± 3.0 116 ± 4.0* *p = 0.011, combination vs. enalapril and vs. losartan at 10 mo; p-values for all other between-group comparisons NS Percent reduction in LVMI from baseline to 10 mo (see Figure 3): Enalapril: 12.4 ± 3.2%* Losartan: 9.1 + 2.1% Enalapril + losartan: 20.5 ± 5.0%** *p < 0.05, enalapril vs. losartan **p < 0.01, combination vs. single treatments **12) Creatinine/GFR:** Creatinine levels (mg%) were in the normal range for all patients and did not change significantly during treatment. There were no significant between-group differences. <u>Baseline</u> <u>10 mo</u> Enalapril (n = 15) 1.2 ± 0.2 1.2 ± 0.3 Losartan (n = 15) 1.1 ± 0.3 1.2 ± 0.3 Enalapril + losartan (n = 16) 1.2 ± 0.3 1.3 ± 0.3 **13) Proteinuria:** NR	
Barnett, Bain, Bouter, et al., 2004 **#1560**	Geographical location: 39 centers in northern Europe (Denmark, Finland, The Netherlands, Norway, Sweden, and the UK)	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 250 - Began treatment: 250 - Completed treatment: 168	**1) Blood pressure:** Adjusted mean reduction in SBP over 5 yr (last observation carried forward): <u>Telmisartan</u> <u>Enalapril</u> 6.9 mm Hg 2.9 mm Hg 95% CI: -8.5 to 0.5 mm Hg	**General comments:** - Primary outcome of study was change in GFR Quality assessment: Overall rating: Fair

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Study dates: NR Funding source: Boehringer Ingelheim Interventions: - Telmisartan 40 mg daily for 4 weeks, then forced titration to 80 mg daily (n = 120) - Enalapril 10 mg daily for 4 weeks, then forced titration to 20 mg daily (n = 130) Additional antihypertensives (not ACEIs or ARBs) allowed after 2 mo if SBP > 160 or DBP > 100 Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: NR Was allocation concealment adequate?: Yes Baseline/run-in period: 1 month – received regular antihypertensive meds including an ACEI (which was then stopped at randomization) Duration of treatment: 5 years Duration of post-treatment followup: NA	- Withdrawals/losses to followup: 38 telmisartan group (20 due to AEs, 18 for other causes), 44 enalapril group (30 due to AEs, 14 for other causes) Age: Mean (SD): 60.6 (8.8) Median: NR Range: NR **Sex (n [%]):** Female: 68 (27%) Male: 182 (73%) Race/ethnicity (n [%]): White: 246 (98.4%) Other: 4 (1.6%) **Baseline blood pressure:** Measured at trough; method of assessment not further described Mean baseline values: <u>Telmisartan</u> <u>Enalapril</u> SBP 152.6 ± 16.6 151.6 ± 15.8 DBP 85.4 ± 8.8 85.9 ± 7.8 **Concurrent medications (n [%]):** Diuretics: 130 (52%) Beta-blockers: 98 (39.2%) Calcium channel blockers: 115 (46%) Other antihypertensive agents: 88 (35.2%) Aspirin: 98 (39.2%) Statins: 105 (42%)	Figure 2 demonstrates changes graphically. % of patients with: SBP < 160: 75% SBP < 140: 42% No significant difference between groups. **2) Rate of use of a single antihypertensive agent for BP control:** Table 2 gives some information, but is imprecise. Based on figures reported, percentages of patients on monotherapy for hypertension during the study were in the following ranges: Telmisartan: 15-65% Enalapril: 18.5-64.6% **3) Mortality:** Deaths: Telmisartan: 6 (3 due to CV events [stroke, MI, or cardiac insufficiency]) Enalapril: 6 (2 due to stroke) **4) Morbidity:** <u>Telmisartan</u> <u>Enalapril</u> Stroke 6 6 CHF 9 7 Non-fatal MI 9 6 Incr Cr < 2.3 2 2 **5) Safety:** <u>Telmisartan</u> <u>Enalapril</u>	Comments: - Many dropouts; GFR data based on data available in only 216 subjects (103 telmisartan, 113 enalapril) **Applicability:** - Patients all with diabetic nephropathy (~80% microalbuminuria, ~20% macroalbuminuria) - Minimal focus on HTN, details of BP assessment not described, and overall targets quite high compared to current recommendations

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Any AE: 115 (95.8%) 130 (100%) AE leading to study discontinuation: 20 (17%) 30 (23%)	
		Comorbidities (n [%]): Duration of diabetes (median [range]): Telmisartan: 8.0 yr (0-25) Enalapril: 8.0 yr (0-37) History of cardiovascular disease: Telmisartan: 59 (49.2%) Enalapril: 63 (48.5%)	**6) Specific adverse events:** See 4) above. Note that patients with know history of angioedema related to ACEIs were excluded. **7) Persistence/adherence:** NR	
		Recruitment setting: Academic centers in northern Europe Inclusion criteria: - White or Asian race/ethnicity - Age 35-80 - Type 2 diabetes treated by diet, diet + oral hypoglycemic drugs (for ≥ 1 year), or insulin preceded by treatment with oral agents (for ≥ 1 year) - For patients treated with insulin, onset of diabetes > age 40 and BMI > 25 at time of diagnosis - History of mild-to-moderate hypertension (mean seated SBP ≤ 180 mm Hg) - Current resting BP < 180/95 mm Hg after ≥ 3 months of treatment with ACEI prior to study entry - Normal gross renal morphology for ≥ 12 months - Urinary albumin excretion rate (mean of 3 consecutive overnight values) of 11-999 μg/min, with 2 values > 10 μg/min	**8) Lipid levels:** Pre-study levels recorded, post-study not given although stated "there were no changes in routine hematologic or blood chemical values in either group." **9) Progression to type 2 diabetes:** NA (all had type 2 diabetes with micro/macroalbuminuria) **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** See Fig 1 & Table 3 for details. Mean change from baseline (last observation carried forward): Telmisartan (n = 103) Enalapril (n = 113) Change (95% CI) GFR -17.5 -15.0 -2.6 (-7.1, 2.0) Telmisartan Enalapril Change	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- HbA1c < 12% - Serum creatinine ≤ 1.6 mg/dL (140 μmol/L) - GFR ≥ 70 mL/min/1.73 m^2 - Women who were < 60 had to be either surgically sterile or have negative pregnancy test at enrollment Exclusion criteria [note – some of these are from a separate article describing methods]: - Renal dysfunction not due to diabetic nephropathy - Single kidney or known renal artery stenosis - New York Heart Association functional class II-IV CHF - Known allergy to study drugs or iohexol - History of angioedema related to ACEIs	(n = 116) (n = 128) (95% CI) Creat 0.10 0.10 0 (-0.66, 0.65) **13) Proteinuria:** Mean change from baseline (last observation carried forward): Telmisartan (n = 115) Enalapril (n = 125) Change (95% CI) UAE* 1.03 0.99 1.04 (0.71, 1.51) *UAE = urinary albumin excretion (ratio)	
Black, Graff, Shute, et al., 1997 **#1561**	Geographical location: NR, but likely U.S. in Illinois, Florida, Texas, or Oregon Study dates: NR Funding source: NR, but one author each affiliated with GFI Pharmaceutical Services and Ciba-Geigy Corporation Interventions: - Valsartan 80 mg with titration to 160 mg once daily (n = 177) - Valsartan 80 mg with titration to 80 mg twice daily (n = 187) - Lisinopril 10 mg with titration to	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 734 - Began treatment: 734 - Completed treatment: 644 - Withdrawals/losses to followup: 90 (“most” due to AEs or unsatisfactory therapeutic response) Age: Mean (SD): 53.5 Median: NR Range: NR **Sex (n [%]):**	**1) Blood pressure:** Mean post-treatment BP values NR Primary outcome = least mean square change in DBP from baseline (all randomized patients, using last available posttreatment BP measurement): Valsartan 80/160: -8.29 mm Hg Valsartan 80/80x2: -8.67 Lisinopril 10/20: -9.97 p = NS Results for change in SBP reported to be comparable (quantitative data NR) Per-protocol results for 12 wk also reported, but only graphically (Figure 2)	**General comments:** Population not well specified, randomization not specified Quality assessment: Overall rating: Fair Comments: - Population not well specified - Method of randomization not described - Potential confounders/comorbidities not discussed - Some important outcomes not assessed; did not report unadjusted posttreatment DBP and

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	20 mg once daily (n = 187) - Placebo (n = 183) Dose titration and co-interventions: Titration allowed after 4 wk for patients with mean seated DBP ≥ 90 and no symptoms of orthostatic hypotension; no co-interventions allowed Study design: RCT, parallel-group Stratified by age Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: NR Baseline/run-in period: 2- to 4-wk placebo run-in Duration of treatment: 12 wk Duration of post-treatment followup: NR	Female: 39% Male: 61% Race/ethnicity (n [%]): White: 81% Black: 14% Other: 4% **Baseline blood pressure:** Trough seated BP measured 3 times each visit after 5-min rest using mercury sphygmomanometer Mean baseline values (± SD): SBP / DBP Valsartan 80/160: 153.64 ± 11.07 / 100.81 ± 4.41 Valsartan 80/80x2: 154.27 ± 14.95 / 101.66 ± 4.83 Lisinopril 10/20: 153.93 ± 14.94 / 100.99 ± 4.45 **Concurrent medications (n [%]):** NR, but no BP lowering meds allowed **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: - Age 21-80 yr	BP response rates (mean DBP < 90 or ≥ 10 decrease from baseline; all randomized patients, using last available posttreatment BP measurement): Valsartan 80/160: 44.1% Valsartan 80/80x2: 48.7% Lisinopril: 10/20: 57.2% p = 0.012 for valsartan 80/160 vs. lisinopril p = NS for valsartan 80/80x2 vs. lisinopril **2) Rate of use of a single antihypertensive agent for BP control:** No additional antihypertensives allowed **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Any AE: Valsartan (any dose): 62.6% Lisinopril (either dose): 58.3% AEs considered to be drug-related: Valsartan: 22.8% Lisinopril: 27.8% Serious AEs and/or withdrawals due to AEs: Valsartan: 14/364 (3.8%) Lisinopril: 8/187 (4.3%) Drug-related AEs leading to withdrawal: Valsartan: 7 (headache 3, lightheadedness 1, shortness of breath 1, rash 1, fatigue 1) Lisinopril: 6 (cough 3, chest pain 1, nausea/dizziness 1, fatigue 1) **6) Specific adverse events:**	SBP values **Applicability:** - Setting not specified, study centers not reported - Unclear how patients recruited - Exclusion criteria vague on what “clinically significant” means

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Stage I-III diastolic HTN (seated DBP ≥ 95 and ≤ 115 after placebo run-in period) Exclusion criteria: - Symptomatic CHF, MI, hypertensive encephalopathy, or CV accident < 6 mo - 2nd or 3rd degree heart block - Angina - Clinically relevant arrhythmias - Clinically significant valvular disease - Significant hepatic disease - Significant renal disease - Insulin-dependent diabetes - Women of childbearing age not using contraception	<table><tr><th></th><th>Valsartan (n = 364)</th><th>Lisinopril (n = 187)</th></tr><tr><td>Headache</td><td>7.7%</td><td>3.2%</td></tr><tr><td>Viral infection</td><td>0.3%</td><td>0%</td></tr><tr><td>URI</td><td>0.5%</td><td>0%</td></tr><tr><td>Fatigue</td><td>2.2%</td><td>3.7%</td></tr><tr><td>Back pain</td><td>0.3%</td><td>0%</td></tr><tr><td>Diarrhea</td><td>1.6%</td><td>2.1%</td></tr><tr><td>Cough</td><td>1.1%</td><td>8.0%</td></tr><tr><td>Dizzy</td><td>1.1%</td><td>3.7%</td></tr><tr><td>Sinusitis</td><td>0.3%</td><td>1.1%</td></tr></table> **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Bloom, 1998 **#1562** ***and*** **Conlin, Gerth, Fox, et al., 2001** **#1570**	Geographical location: Throughout US Study dates: Jul 1995 to Jun 1996; subsequent study reported followup to Jun 2000 Funding source: Merck & Co., Inc. Interventions: ARB (n = 567)	Number of patients: - Screened for inclusion: 1.3 to 1.6 million - Eligible for inclusion: NA - Randomized: NA - Began treatment: 21,723 - Completed treatment: NA - Withdrawals/losses to followup: 6548 lost by 4-year followup Age: Mean (SD): 56 (NR)	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR	**General comments:** - The large sample size and representative population of the PBM database are strengths of the study, but rating is downgraded because of lack of specificity regarding hypertensive diagnosis and comorbidity, as well as no dose info; correlation between dose and BP response and change in prescription - Reasons for discontinuing

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	ACE inhibitor (n = 5842) CCB (n = 5094) Beta-blocker (n = 4994) Thiazide diuretic (n = 5226) Study design: Retrospective cohort study Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: NA Baseline/run-in period: NA Duration of treatment: NA Duration of post-treatment followup: 4 yr	Median: NR Range: 35-71 **Sex (n [%]):** Female: 12,148 (55.9%) Male: 9575 (44.1%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** 0 [0%] (not allowed) **Comorbidities (n [%]):** NR (attempted to eliminate subjects with comorbid conditions based on concurrent prescriptions) **Recruitment setting:** Enrollees in pharmacy benefit management program which includes HMO, Blue Cross-Blue Shield, and union, corporate, and government clients Inclusion criteria: - Patients filling first antihypertensive drug prescription in one of 5 classes (ARB, ACEI, CCB, beta-blocker, thiazide) during study period - No prescription filled for any antihypertensive drug in prior 12 mo Exclusion criteria: - Prescription for nitrate,	**6) Specific adverse events:** NR **7) Persistence/adherence:** Based on prescription refill on or within 3 mo after 1-yr anniversary of initial prescription 1-year data: Drug / Continued / Switched / D/c'd ARB / 64% / 7% / 29% ACEI / 58% / 9% / 33% CCB / 50% / 9% / 41% Beta-B / 43% / 7% / 50% Thiaz / 38% / 6% / 56% In multivariable analysis: - Age ≥ 65 years was associated with higher persistence than age between 40 and 64 years (OR, 0.79; 95% CI, 0.74 to 0.84; p = 0.001) and age < 40 years (OR, 0.32; 95% CI, 0.29 to 0.35; p = 0.0001) - Dosing more than once daily was associated with lower persistence than once-daily dosing (OR, 1.40; 95% CI, 1.29 to 1.52; p = 0.0001) 4-year data: Drug / Continued / Switched / D/c'd ARB / 50.8% / 16.5% / 32.7% ACEI / 46.5% / 18.9% / 34.6% CCB / 40.7% / 19.3% / 40.0% Beta-B / 34.7% / 12.7% / 52.6% Thiaz / 16.4% / 32.6% / 51.0% - Persistence with ARB (92% losartan) was higher than persistence with CCBs, beta-blockers or thiazides (p < 0.03), but not higher than ACEI (p = 0.095). - Persistence was higher among women	therapy are not captured (ineffective? adverse events?) - ARBs were introduced just 1 year before the study period, suggesting that prescribing patterns may have been in flux – may not be representative of current patterns Quality assessment: Overall rating: Fair Comments: - Appears to be well done study for administrative database **Applicability:** - Lack of clinical data on subjects means that baseline BP data, BP response, actual comorbidities are unknown

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		antiarrhythmic, digoxin, warfarin, loop diuretic, or certain anti-migraine drugs - Concurrent prescriptions for two or more antihypertensive drug classes (including combination products) - Incomplete data on age and sex	than men, and higher among patients ≥ 65 years of age than those < 65 years of age **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Bourgault, Senecal, Brisson, et al., 2005 **#1563**	Geographical location: Saskatchewan, Canada (database including > 90% of provincial residents) Study dates: Jan 1994-Sep 1999 Funding source: Merck Frosst Canada, Ltd. Interventions: Number of patients with data for at least 180 days: ARBs (n = 1002) ACEIs (n = 7104) Beta-blockers (n = 3989) CCBs (n = 2400) Diuretics (n = 6831) Study design: Retrospective cohort study Blinding: - Patients: No	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: 21,326 - Randomized: NA - Began treatment: NA - Completed treatment: NA - Withdrawals/losses to followup: NA Age (ARBs and ACEIs): Mean: 57.6 Median: NR Range: NR **Sex (ARBs and ACEIs; %):** Female: 45.7% Male: 54.3% Race/ethnicity (n [%]): NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):**	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Sample sizes at various timepoints: ARBs / ACEIs 1 year 463 / 3456 2 years 148 / 1541 3 years 5 / 265	**General comments:** - Cohort studied overlaps with that studied in Marentette, Gerth, Billings, et al., 2002 (#12830); includes fewer total patients, but many more taking ARBs Quality assessment: Overall rating: Fair Comments: - Non-random allocation to drugs - No data on comparability of patients on ACEIs versus ARBs - Funded by pharmaceutical company **Applicability:** - Study period soon after introduction of ARBs; early use may not reflect current use patterns

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: NA Baseline/run-in period: NA Duration of treatment: NR Duration of post-treatment followup: Mean length of followup in ARB and ACEI groups = 1.85 yr	NR **Comorbidities (n [%]):** NR **Recruitment setting:** Population-based prescription drug database Inclusion criteria: - ICD-9 code diagnosis of hypertension (401, 402, 403, 404, or 4-digit codes included in these categories) - Age 18-80 yr - New dispensed antihypertensive med between Jan 1997 and Sep 1999 - Antihypertensive prescribed was ARB, ACEI, beta-blocker, CCB, or diuretic Exclusion criteria: - Prescribed more than one antihypertensive agent at treatment initiation	Persistence defined as continuously refilling a prescription for any antihypertensive drug within 90 days of previous dispensing (assumed to last 15-30 days), regardless of switches across drug classes and add-on therapies. Cumulative persistence: <u>ARBs</u> <u>ACEIs</u> 1 year 66% 59% 2 years 56% 47% 3 years 53% 40% Similar results were observed after controlling for age and sex, which were not explicitly noted as being statistically significant. Note: “Persistence” includes combinations and switches; in essence, what is being modeled is failure to discontinue. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Burke, Sturken-boom, Lu, et al., 2006 **#1565**	Geographical location: 694 general practices widely distributed across the UK (less coverage in Scotland and inner London) Study dates: Jan 1991 – Mar 2002 Funding source: Merck & Co., Inc. Interventions: Numbers reported below are the % of patients given a drug from the specified class as their first prescription and the total number of "drug class episodes," respectively ACEI (12.2%; 36,386) ARB (0.5%; 5184) α-antagonist (1.1%; 7823) Beta-blocker (27.4%; 54,973) CCB (12.5%; 41,019) Potassium-sparing diuretic (0.2%; 1831) Thiazide (42.0%; 71,331) Miscellaneous monotherapy (0.3%; 4681) Combination (3.7%; NA) Study design: Retrospective cohort study Blinding: - Patients: No - Providers: No - Assessors of outcomes: No	Number of patients: - Screened for inclusion: > 9 million - Eligible for inclusion: 109,454 - Randomized: NA - Began treatment: 109,454 - Completed treatment: NA - Withdrawals/losses to followup: NA Age: Mean (SD): 60.6 (13.4) Median: NR Range: < 50 22.4% 50-59 25.1% 60-69 25.5% ≥ 70 27.0% **Sex (n [%]):** Female: 56.5% Male: 43.5% Race/ethnicity (n [%]): NR **Baseline blood pressure:** Mean SBP (± SD): 173.5 ± 21.1 Mean DBP (± SD): 99.7 ± 27.3 **Concurrent medications (n [%]):** NR; patients with pre-existing diabetes prescription excluded **Comorbidities (n [%]):** NR; patients with pre-existing diabetes diagnosis excluded **Recruitment setting:** UK General Practice Research	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Discontinuation was analyzed based on a Kaplan-Meier analysis of time until 90+ days passed without a refill. Investigators also performed a Cox regression using the same outcome variable and controlling for various patient factors (age, number of previous antihypertensive drug classes, calendar year of antihypertensive therapy initiation, pretreatment SBP, duration of hypertension, smoking). The results of this modeling are substantially similar to the unadjusted analysis presented immediately below. Cumulative discontinuation rates: 1 yr 2 yr 3 yr 4 yr ACEIs 37.8% 48.0% 54.8% 60.4% ARBs 29.4% 41.3% 50.3% 57.8% α-antag 44.7% 56.5% 64.4% 69.9% BB 44.0% 54.3% 61.2% 66.7% CCB 41.2% 51.5% 58.8% 64.7%	**General comments:** - Outcomes of interest were analyzed on the basis of the number of drug-class episodes (223,228), not number of patients (109,454) Quality assessment: Overall rating: Poor Comments: - Non-random allocation to drugs - Time period of study includes considerable period before ARBs were available; allocation of patients to ACEIs versus ARBs may as a result be biased - No measurement, reporting, or adjustment for potential confounders - No data on comparability of patients on ACEIs versus ARBs **Applicability:** - UK location and different health system may affect use rates/patient characteristics - Study period soon after introduction of ARBs; early use may not reflect current use patterns - Specific ACEIs and ARBs not identified - Diabetics excluded

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Was allocation concealment adequate?: NA Baseline/run-in period: NA Duration of treatment: NA Duration of post-treatment followup: 4 yr	Database. Contains information (demographic descriptors, information from GP visits, GP prescription data [used to generate written prescriptions], diagnoses from specialist referrals and hospital admissions, and lab results) on > 9 million patients. Inclusion criteria: - Age ≥ 18 - New physician diagnosis of hypertension between 1 Jan and 31 Dec 2001 ("new" diagnosis = no hypertension diagnoses prior to 1 Jan 1991 and no antihypertensive prescription within 1 year of new diagnosis) Exclusion criteria: - Diabetes diagnosis or diabetes prescription before antihypertensive prescription	K-diuretic 64.1% 74.9% 81.1% 84.9% Thiazide 43.9% 55.4% 63.1% 69.3% Misc 62.8% 75.0% 81.1% 84.8% Switching was defined only for the subset of patients that discontinued their first line antihypertensive: ACEIs 44.2% ARBs 36.5% α-antag 38.2% BB 44.8% CCB 43.4% K-diuretic 30.4% Thiazide 44.6% Misc 25.9% Even though the investigators' modeling controlled for various patient characteristics, it was not possible to determine which of these characteristics were predictive of persistence. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Celik, Iyisoy,	Geographical location: NR (author based in Turkey)	Number of patients: - Screened for inclusion: NR	**1) Blood pressure:** At 6 months, n = 50 each group:	**General comments:** None

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Kursak-lioglu, et al., 2005 **#1566**	Study dates: NR Funding source: NR Interventions: - Ramipril 10 mg (n = 50) - Telmisartan 80 mg telmisartan (n = 50) Study design: RCT, parallel-group Blinding: - Patients: NR - Providers: NR - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: NR Duration of treatment: 6 months Duration of post-treatment followup: NR	- Eligible for inclusion: NR - Randomized: 100 - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR Age: Mean (SD): 51.79 ±6.01 Median: NR Range: NR **Sex (n [%]):** Female: 44 (44%) Male: 56 (56%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** BP measured 3 times after a 10-min resting period using a standard mercury sphygmanometer; mean of 3 measurements used Telmisartan / Ramipril SBP 155.9 ± 6.75 / 154.3 ± 5.44 DBP 96.4 ± 6.47 / 94.7 ± 5.83 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** DM: 17 (17%) Family history of premature CAD: 19 (19%) Smoking: 26 (26%)	Telmisartan / Ramipril / p-value SBP 133.5 ± 9.48 / 130.4 ± 13.39 / 0.18 DBP 81.4 ± 6.06 / 80.2 ± 7.75 / 0.39 **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** Atrial fibrillations occurred in 4 patients in enalapril arm and 2 patients telmisartan arm **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** LVEF Telmisartan / Ramipril Before 61.58 ± 2.06 / 61.96 ± 1.87 After 61.70 ± 1.54 / 61.94 ± 1.40 **12) Creatinine/GFR:** NR	Quality assessment: Overall rating: Poor Comments: - Significant missing data – timing, funding of study, the number screened, the number that completed treatment - Study and assessment were not blinded; may lead to bias - No data on safety/adverse events **Applicability:** - Many common conditions excluded - No information on number screened or recruitment setting - No data on race/ethnicity of subjects

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			13) Proteinuria: NR	
		Recruitment setting: NR Inclusion criteria: 100 newly diagnosed hypertensive patients without the below exclusions Exclusion criteria: - Secondary or malignant hypertension - Chronic obstructive lung disease - Atrial fibrillation, flutter, or any other atrial tachyarrhythmia's with 1 month - History of anti-arrythmic drugs, including digoxin, within 1 month - Hyperthyroidism - Severe valvular disease of hemodynamic significance - History of sensitivity to use of ACEIs or ARBs - Pregnancy or nursing - MI or cerebrovascular accident within 6 months - History of proven coronary artery disease - Concurrent therapy with medication that could affect blood pressure - Severe renal or hepatic failure		
Coca, Calvo, Garcia-Puig, et al., 2002 **#1569**	Geographical location: Multicenter trial: 17 centers in Spain Study dates: NR Funding source: Sanofi-	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: 295 - Randomized: 238 - Began treatment: 238 - Completed treatment: 226 - Withdrawals/losses to followup:	**1) Blood pressure:** Posttreatment seated trough BP values not reported ABPM results: 24-hr BP at 12 wk: Irbesartan Enalapril	**General comments:** - Baseline 24-hour SBP significantly higher in irbesartan group (mean 4 mm p = 0.003) Quality assessment: Overall rating: Fair

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Synthelabo Spain Interventions: Doses (titrated doses if DBP ≥ 90 after 4 or 8 weeks of treatment): - Irbesartan 150 mg/d (300 mg); n = 111, dose titration in 80 (72%) - Enalapril 10 mg/d (20 mg); n =115, dose titration in 88 (76.5%) Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: NR - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: 3-wk single-blind placebo phase; patients with mean daytime DBP < 85 mm Hg during this period were excluded Duration of treatment: 12 weeks Duration of post-treatment followup: 24 hours after last dose of study medication	12 (5 due to AEs, 4 lost to followup, 3 due to lack of efficacy) Age: Mean (SD): 52.7 ± 10.6 yr Median: NR Range: 22-73 **Sex (n [%]):** Female: 52% Male: 48% Race/ethnicity (n [%]): 100% white **Baseline blood pressure:** *Clinic BP* using mercury sphygmo-manometer: After resting for 10 minutes in seated position; non-dominant arm supported and cuff arm at heart level. 3 successive readings at 3 min intervals, mean of 3 values recorded. Irbesartan / Enalapril SBP 160.3 ± 14.1 / 158.2 ± 13.8 DBP 101.6 ± 4.7 / 102.0 ± 5.2 *24-hr ABPM* using a non-invasive automated oscillometric device (Spacelabs 90207); cuff placed on non-dominant arm, BP recorded at 20-min intervals automatically for 24 hr Irbesartan (n = 115) / Enalapril (n = 123)	(n = 111) / (n = 115) SBP 128.8 ± 13.8 / 127.2 ± 11.1 DBP 79.9 ± 8.8 / 80.5 ± 8.1 Baseline and 12-wk mean BPs also reported for ambulatory daytime BP (= average 10 a.m. to 8 p.m.) and nighttime BP (average 12 – 6 a.m.) Mean reductions in 24-hr ABPM BP: Irbesartan (n = 111) / Enalapril (n = 115) SBP 14.7 ± 14.7 / 12.6 ± 13.1 DBP 9.4 ± 8.5 / 8.8 ± 8.5 Between-group p-value NS Mean reductions in seated trough BP: Irbesartan (n = 111) / Enalapril (n = 115) SBP 19.0 ± 14.1 / 17.5 ± 14.0 DBP 12.7 ± 8.8 / 12.4 ± 7.4 Between-group p-value NS Seated trough BP – response rates: 36% (40/111) of patients treated with irbesartan and 34.8% (40/115) of those treated with enalapril achieved strict BP control (clinic BP < 140/90 at 12 wk). Response rates based on the clinic criterion (DBP reduction of ≥ 10 mm Hg at 12 wk) were 64.0% (71/11) and 67.8% (78/115), respectively. 24-hr ABPM – response rates:	Comments: - Very little baseline information - Randomization process not described - Patients who failed treatment (BP ≥ 180/110 despite full-dose treatment) excluded (n = 3) **Applicability:** - All white patients - Recruitment setting not clearly described - Process of inclusion of study centers not described - Comorbid conditions not described: they were “excluded” but list of criteria not mentioned

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		SBP 144.2 ± 11.5 140.1 ± 11.9 DBP 89.9 ± 6.3 89.6 ± 7.9 **Concurrent medications (n [%]):** No other antihypertensives or any other drugs with effects on the cardiovascular system permitted **Comorbidities (n [%]):** NR; patients with severe concomitant disease excluded **Recruitment setting:** NR Inclusion criteria: Mild-moderate hypertension (clinic DBP 90-109 mm Hg on ≥ 3 occasions, SBP 140-179 mm Hg or uncontrolled hypertension (BP ≥ 140/90) despite monotherapy with antihypertensive drugs other than ACE inhibitors or ARBs Exclusion criteria: - Renal impairment (Ser Cr > 1.5 mg/dL), papilledema, or evidence of coronary heart disease or cardiac failure during the previous 3 months - Severe concomitant disease - Women who were pregnant or of childbearing potential	40.5% (45/111) of patients with irbesartan and 33.9% (39/115) with enalapril achieved strict BP control (daytime BP < 130/85 at 12 wk), with no significant difference between groups. Response rates (reduction in 24-hr DBP of ≥ 5 mm Hg at 12 wk independent of clinic values) were 71.2% (79/111) and 71.3% (82/115), respectively. **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Irbesartan n (%) / Enalapril n (%) Any AE: 46 (40) / 63 (51.2) Discontinued d□e to AEs: 2 (1.7) / 3 (2.4) AEs deemed probably related to treatment were less frequent with irbesartan than with enalapril (9.2% vs. 24.6%, p = 0.026) Risk of AEs deemed probably related to treatment: 2.6 times higher in those treated with enalapril (OR 2.6, 95% CI 1.1 to 6.1) Discontinued due to AEs in irbesartan group (n = 2): GI disturbance, nausea, vomiting Discontinued due to AEs in enalapril group (n = 3): skin rash, persistent cough	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

6) Specific adverse events:

Most common AEs (> 5% in either group):

	Irbesartan (%)	Enalapril n (%)
Nervous system	22 (19.1)	33 (26.8)
Fatigue, back pain, fever	16 (13.9)	10 (8.1)
GI system	12 (10.4)	8 (6.5)
Headache	11 (9.6)	18 (14.6)
Dizziness	9 (7.8)	17 (13.8)
Cardiovascular system	8 (7.0)	9 (7.3)
Palpitations	7 (6.1)	8 (6.5)
Upper resp tract	4 (3.5)	18 (14.6)
Cough	1 (0.9)	10 (8.1)
Skin disorders	-	5 (4.1)

7) Persistence/adherence:
Compliance with treatment (assessed by pill counts at each visit) similar in two groups: 98.3% in patients treated with irbesartan and 98.4% in those treated with enalapril

Irbesartan once daily better tolerated than enalapril once daily

8) Lipid levels: NR

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td></td><td></td><td>metabolism/diabetes control: NR

11) LV mass/function: NR

12) Creatinine/GFR: NR

13) Proteinuria: NR</td><td></td></tr>
<tr><td>Cotter, Oliveira, Cunha, et al., 2008

#66</td><td>Geographical location: Guimaraes, Portugal

Study dates: Jan 2004-June 2005

Funding source: NR

Interventions:
Treatment with either ACEIs (n = 40) or ARBs (n = 31)

ACEIs used were lisinopril (20 mg/d) or ramipril (10 mg/d)

ARBS used were irbesartan (300 mg/d) or valsartan (160 mg/d)

Were additional anti-hypertension medications allowed: Yes as long not an ACEI (in the ARB group) or an ARB (in the ACEI group)

If Yes to above, was this done: At discretion of clinician/investigator

Study design: Other – prospective longitudinal observational study</td><td>Number of patients: N = 71
- Screened for inclusion: NR
- Eligible for inclusion: NR
- Randomized: NA
- Began treatment: 71
- Completed treatment: 71
- Withdrawals/losses to followup: 0

Age:
Mean (SD): 57.4 ± 13.7

Sex (n [%]):
Female: 39 (54.9%)
Male: 32 (45.1%)

Race/ethnicity (n [%]): NR

Baseline blood pressure:
Automatic Omron M4-1 device with patient resting seated for at least 10 minutes, measured 3 times during visit and mean of last two measurements taken as blood pressure value

ARB baseline:
SBP 148.5 ± 16.3
DBP 86.7 ± 15.2

ACEI baseline:
SBP: 154.5 ± 20.7</td><td>1) Blood pressure:
12-month followup – note that all patients are on ACE or ARB at baseline, so these findings should not be combined with other studies reporting blood pressure lowering outcome

ARB:
SBP: 148.5 ± 20.5
DBP: 89.1 ± 13.5

ACEI baseline:
SBP: 149.3 ± 19.1
DBP: 87.5 ± 10.0

2) Rate of use of a single antihypertensive agent for BP control:
States that there were no differences between the groups in the mean of prescribed antihypertensive drugs, statins, or antiplatelets, or in the presence in each group of other classes of antihypertensive drugs prescribed

3) Mortality: None

4) Morbidity:

<table>
<tr><td>Comorbidity</td><td>ARB</td><td>ACEI</td></tr>
<tr><td>BMI</td><td>30.9 ± 5.6</td><td>27.9 ± 4.2*</td></tr>
<tr><td>GFR</td><td>75.9 ± 19.8</td><td>64.2 ±</td></tr>
</table>
</td><td>General comments:
- Does not provide information on how long patients were on treatment prior to observational study
- Goal of study is evaluate the evolution of urinary albumin excretion in hypertensive patients with microalbuminuria undergoing ACEI or ARB treatment

Quality assessment:
Overall rating: Fair

Comments: None

Applicability:
- All patients were on “ongoing treatment” with an ACE or ARB at baseline, so blood pressure changes do not reflect a new treatment start
- Does not discuss crossovers or whether treatment was discontinued for any reason
- Does not describe adverse events related to treatment</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Blinding:
- Patients: No
- Providers: No
- Assessors of outcomes: No

Was allocation concealment adequate?: NA

Baseline/run-in period: NA

Duration of treatment: 12 months (total)

Duration of post-treatment followup: 12 months (total)

DBP 85.8 ± 13.6

Concurrent non hypertension medications (n [%]):
States that there were no differences between the groups in the mean of prescribed antihypertensive drugs, statins, or antiplatelets, or in the presence in each group of other classes of antihypertensive drugs prescribed

Comorbidities (n [%]):
No significant differences in comorbidities other than BMI (higher in the ARB treatment group) and glomerular filtration rate (higher in ARB group)

Specific numbers listed below:

Co-morbidity	ARB	ACEI
Diabetes	25 (80.6%)	27 (67.5%)
Smokers	7 (22.5%)	3 (7.5%)
BMI	30.8 ± 5.7	27.7 ± 4.0*
GFR (MDRD)	76.6 ± 20.7	66 ± 18.7*
GFR (Cock-croft-Gault)	97.8 ± 39.9	73.9 ± 27.8*
HbA1c	7.2 ± 1.9	7.8 ± 1.7
Stroke	5 (16.1%)	8 (20%)
IHD	2 (6.5%	5
(MDRD)		18.8*
GFR (Cockcroft-Gault)	96.1 ± 41.8	72.1 ± 27.8*
HbA1c	7.5 ± 1.8	7.7 ± 1.6
Stroke	5 (16.1%)	9 (22.5%)
IHD	3 (9.7%	5 (12.5%)
HF	4 (12.9%)	5 (12.5%)
PAD	7 (22.6%)	7 (17.5%)

5) Safety: NR

6) Specific adverse events: NR

7) Persistence/adherence: NR

8) Lipid levels: NR

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: See above table (under "Morbidity")

11) LV mass/function: NR

12) Creatinine/GFR: See table above (under "Morbidity")

13) Proteinuria: NR

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		(12.5%) HF: 3 (9.7%) / 5 (12.5%) PAD: 6 (16.1%) / 5 (12.5%) * P < 0.05. **Recruitment setting:** Outpatient hypertension clinic of a hospital serving a population of about 300,000 Inclusion criteria: Study included all patients who attended hospital HTN clinic during study dates with confirmed HTN and microalbumineria and an estimated creatinine clearance of ≥ 29 mL/min as determined by the simplified MDRD equation and who were undergoing treatment with either ACEIs or ARBs (but not both). Subjects treated with ACEIs were never treated with ARBs and vice versa. Exclusion criteria: NR		
Cuspidi, Muiesan, Valagussa, et al., 2002 **#1478**	Geographical location: 36 sites in Italy, France, Germany Study dates: NR Funding source: Takeda Italia Interventions: - Candesartan 8-16 mg qd (n = 115)	Number of patients: - Screened for inclusion: 304 - Eligible for inclusion: 239 - Randomized: 239 - Began treatment: 239 - Completed treatment: 182 - Withdrawals/losses to followup: 57 (19 due to AEs, 12 withdrew consent, 14 lack of efficacy, 12 "other")	**1) Blood pressure:** BP was measured at the end of placebo period and at 4, 8, 12, 24, 36, and 48 weeks Mean post-treatment BP values NR Mean changes in SBP and DBP from baseline to last available timepoint (ITT population): No significant difference between the two treatments (no quantitative	**General comments:** - Emphasis on a non-biased approach and interpretation of results Quality assessment: Overall rating: Fair Comments: - Would have been compelling if

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Enalapril 10-20 mg qd (n = 124) Dose titration/co-interventions: - Higher dose of study drug used after 4 wk if BP not controlled (≥ 140/90 mmHg or DBP reduced < 10 mmHg and SBP < 20%) -After 4 additional wk, if BP not controlled, HCTZ 12.5 mg added and titrated up to 25 mg as needed Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: Yes Baseline/run-in period: 2- to 4-week run-in with single-blind placebo, previous antihypertensive treatments withdrawn Duration of treatment: 48 weeks Duration of post-treatment followup: NA	- ITT population = 196 - Per-protocol population = 145 Age: Mean (SD): 52.9 Median: NR Range: NR **Sex (n [%]):** Female: 74/196 (38%) Male: 122/196 (62%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Seated trough BP measured using a mercury sphygmomanometer; 3 readings taken at 1-min intervals after patient seated for 5 min of rest. Mean of 3 readings used. Candesartan (n = 91) / Enalapril (n = 105) SBP 163.1 ± 9.7 / 162.4 ± 8.9 DBP 101.5 ± 3.9 / 101.0 ± 4.4 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: - Age 25-70 yr - Hypertension (SBP 150-200	data or statistical tests shown) Similar results (no significant between-group differences) for mean changes in SBP and DBP at 24 and 48 wk in the per-protocol population (no quantitative data or statistical tests shown) The percentage of patients achieving BP normalization (defined as < 140/90 mmHg): Candesartan: 60.4% Enalapril: 60.0% No statistical testing shown; not clear whether ITT or per-protocol population **2) Rate of use of a single antihypertensive agent for BP control:** ITT analysis (n = 196 patients) Patients receiving study drug alone (with no HCTZ): Candesartan: 54.3% Enalapril: 45.8% Per-protocol analysis (n = 145 patients) Patients receiving study drug alone (with no HCTZ): Candesartan: 61.0% Enalapril: 53.4% **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** There were no serious AEs Adverse events: N (%) / Withdrawals (n) Candesarta: 16 (14%) / 6	article included the mean BP measurements taken at 4, 8, 12, 24, 36, and 48 wk - May be error in randomization, as female low in the enalapril group (34% vs. 42% in candesartan group) **Applicability:** - No data on race/ethnicity of subjects - Restricted to patients with LVH

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

mm Hg and DBP 95-115 mm Hg at end of placebo run-in period)
- LVH (LVMI > 120g/m^2 in men and LVMI > 100g/m^2 in women)

Exclusion criteria:
- Adequate M-mode echo cardiogram not obtained
- Clinical or echocardiographic evidence of significant valvular disease
- Coronary heart disease
- CHF
- Dilated LV chamber (end diastolic diameter > 60 mm)

n		
Enalapril	24 (19%)	13

6) Specific adverse events:
Cough occurred in 9% of enalapril patients and in 3% of candesartan patients

7) Persistence/adherence: Compliance measured by counting return tablets; no results reported.

8) Lipid levels: NR

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: NR

11) LV mass/function: LV mass estimated by Devereux's formula and normalized for body surface

LVMI (g/m^2) measurements by echocardiographic and Doppler (ITT population):

	Baseline	Treatment (last available timepoint)
Candesartan (n = 91)	141.0 ± 24.1	126.0 ± 32.4
Enalapril (n = 105)	143.4 ± 27.5	130.1 ± 29.3

The decrease in LV mass was accomplished by substantial reduction in interventricular septum and posterior wall thickness in both treatment groups.

12) Creatinine/GFR: NR

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			13) Proteinuria: NR	
De Rosa, Cardace, Rossi, et al., 2002 **#1571**	Geographical location: Naples, Italy Study dates: NR Funding source: NR Interventions: - Enalapril 5-20 mg (n = 24) - Losartan 12.5-50 mg (n = 26) Dose titration: - Enalapril started at 5 mg daily, titrated q 7 days, as tolerated, to 10 mg and 20 mg daily if DBP ≥ 90 - Losartan started at 12.5 mg daily, titrated q 7 days, as tolerated, to 25 mg and 50 mg daily if DBP ≥ 90 No co-interventions permitted Study design: RCT, parallel-group Blinding: - Patients: Yes (double-dummy) - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: NR Baseline/run-in period: 2-wk placebo run-in	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 50 - Began treatment: 50 - Completed treatment: 42 - Withdrawals/lost to followup: 8 (3 due to AEs, 2 lost to followup, 2 non-responders, 1 other) Age: *For randomized group n = 50* - Mean (SD): 52 yrs (7.7) - Median: NR - Range: NR *For analyzed group completing study n = 42* - Mean: 55 (SD not reported) - Range: 52-62 - **Sex (n [%]):** (#s given are for analyzed 42 pts) Female: 21 (50%) Male: 21 (50%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Trough seated BP measured using a standard mercury sphygmomanometer after 5 min rest; average of 3 readings taken at 1-min intervals <u>Losartan</u> <u>Enalapril</u> SBP	**1) Blood pressure:** Seated trough mean difference in BP (95% CI) at 3 yrs: p value - NS Losartan (n = 22) Pre- 155/103 Post- 140/92 Mean diff SBP -14.5mmHg (-22.6, -6.4) Mean diff DBP -10.5mmHg (-13.5, -7.6) Enalapril (n = 20) Pre- 159/102 Post- 144/91 Mean diff SBP -14.6 (-27.4, -1.7) Mean diff DBP -11.4 (-14.8, -8.1) **2) Rate of use of a single antihypertensive agent for BP control:** NA (no other antihypertensive meds permitted) **3) Mortality:** NR **4) Morbidity:** No quantitative data reported. Number of patients assessed unclear for most measures. QOL: "battery-of-scales" QOL instrument at baseline and after 12 wk of therapy. There were no statistical differences between the two therapies in the domains of general health, sexual functioning, or for the other scales of quality of life. For symptom bother, there was no between-group difference in HA or flushing,	**General comments:** - 2/26 pts in losartan group withdrew due to ineffective therapy and were excluded from analysis; 0/24 were excluded from enalapril for this reason. This biases BP results in losartan's favor. Quality assessment: Overall rating: Fair Comments: See comments above and below. **Applicability:** - Small number of patients from single center in Italy - Minimal information on patient characteristics - Analyzed according to treatment completion and excluded those in whom therapy was ineffective

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		155 ± 17 159 ± 19 DBP 103 ± 4 102 ± 5 **Concurrent medications (n [%]):** NR; no non-study antihypertensives permitted **Comorbidities (n [%]):** See Exclusion criteria (below); otherwise NR **Recruitment setting:** Outpatient clinic Inclusion criteria: - Essential HTN - WHO stage II (SBP >140 and/or DBP > 90) Exclusion criteria: - Sig cardiovascular, cerebrovascular, renal, or hepatic disease. - Recent MI - Secondary HTN - "Clinically significant lab abnormalities"	but there was a significantly higher incidence of "bother due to cough" in the enalapril patients than in losartan patients after 3 years of treatment, regardless of whether the symptom was present at baseline (12% vs. 2%; p = 0.01). **5) Safety:** Withdrawals due to AEs: Losartan: 0/26 Enalapril: 3/24 (12.5%) **6) Specific adverse events:** In patients completing treatment (n = 42), frequency of cough was: - Losartan 2% - Enalapril 12% (p = 0.01) **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** LV mass index change pre-/post- (baseline to 3 yr) using 2-D echocardiogram (g/m^2): Change Pre- Post- (95% CI) Losartan: 176 ± 24 124 -52 (-110.5, 32) Enalapril: 170 ± 19 129 -41(-90.3, 21.9) P-value for between-group difference NR **12) Creatinine/GFR:** GFR measured by renal scintigraphy at	
	Duration of treatment: 3 years Duration of post-treatment followup: NA			

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			baseline and 3 yr (mL/min ± SD): Losartan: Baseline 96.5 ± 32.3; 3 yr 108.6 ± 31.1 Enalapril: Baseline 94.8 ± 31.1; 3 yr 99.8 ± 19.6 P-value: < 0.005 (Losartan); 0.085 (Enalapril) **13) Proteinuria:** NR	
Degli Esposti, Degli Esposti, Valpiani, et al., 2002 **#1573** **(1-year results)** ***and*** **Degli Esposti, Sturani, Di Martino, et al., 2002** **#1572** **(3-year results)**	Geographical location: Ravenna, Italy (databases of a local health unit) Study dates: Jan-Dec 1997 Funding source: Local health unit and Merck Sharp & Dohme Italia S.p.A. Interventions: ACEIs (n = 4986) ARBs (n = 317) CCBs (n = 4680) Diuretics (n = 4341) Beta-blockers (n = 2459) Study design: Retrospective cohort study Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: NA Baseline/run-in period: NA	Number of patients: - Screened for inclusion: 19,124 - Eligible for inclusion: 16,783 - Randomized: NA - Began treatment: NA - Completed treatment: NA - Withdrawals/losses to followup: NA Age (ACEIs and ARBs): Mean: 56.1 Median: NR Range: 20-105 **Sex (ACEIs and ARBs, %]):** Female: 52.6% Male: 47.4% Race/ethnicity (n [%]): NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** ACEIs ARBs Cardiopathy 1.3% 0.9%	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Persistence described under heading of "continuing," "switching," and "discontinuing" therapy; arbitrary minimum of 273 days used as cutoff. Continuing defined as persisting with original drug therapy, even if combined with an agent from another class. Switching defined as persisting with drug treatment, but switching to a drug of a different class. Discontinuing defined as giving up drug therapy altogether.	**General comments:** - Small sample sizes for ARBs at 1 year (n = 317) and 3 years (n = 198) Quality assessment: Overall rating: Fair Comments: - Non-random allocation to drugs - No data on comparability of patients on ACEIs versus ARBs - Funded by pharmaceutical company **Applicability:** - Study period soon after introduction of ARBs; early use may not reflect current use patterns

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Duration of treatment: NR Duration of post-treatment followup: Data reported for 1 and 3 years	Diabetes 2.1% 1.3% Asthma/COPD 1.2% 1.3% Previous hosp for CV disease 7.9% 8.2% ≥ 2 comorbidities 1.6% 3.2% **Recruitment setting:** Database of local health unit Inclusion criteria: - New user of antihypertensive drug (not prescribed any antihypertensive drugs during previous 12 mo) - Age ≥ 20 years - Received first prescription for a diuretic, beta-blocker, CCB, ARB, or ACEI during study period Exclusion criteria: - Prescriptions for ≥ 2 antihypertensive agents or for a combination agent involving ≥ 2 classes - History of ≥ 3 prescriptions for cardiovascular, antidiabetes, or antiasthmatic/COPD drugs over previous 12 mo	1-year data: Continue Switch Discontinue ACEIs 30.7% 9.4% 59.9% ARBs 33.4% 24.6% 42.0% Persistence was related to older age, taking medication for heart disease or diabetes, history of previous hospitalizations for CV events, and presence of ≥ 2 comorbidities 3-year results: No quantitative data reported. Persistence was related to older age, young general practitioner, male general practitioner, and male sex. ARBs had better persistence throughout the followup period, but precise estimates could not be derived from Figure 2. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Delea, Taneja, Moynahan, et al., 2007 **#196**	Geographical location: 70 health plan databases across US Study dates: Jan 1, 1997-Dec 31, 2003	Number of patients: N = 29,357 - Screened for inclusion: 1,482,294 - Eligible for inclusion: 244,512 - Randomized: NA - Began treatment: 244,512	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR	**General comments:** Does not describe effect on BP; focus is on cardiovascular and renal events Quality assessment:

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Funding source: Novartis Pharmaceuticals Corporation Interventions: Valsartan (n = 6645) Lisinopril (n = 17,320) Extended-release metoprolol (not described further here) Were additional anti-hypertension medications allowed: Yes (but not other study drug) If Yes to above, was this done: At discretion of clinician/investigator Study design: Other – retrospective study Blinding: - Patients: NA - Providers: NA - Assessors of outcomes: NA Was allocation concealment adequate?: NA Baseline/run-in period: NA Duration of treatment: Maximum follow up was approximately 70 months in both groups Duration of post-treatment followup: NA	- Completed treatment: NA - Withdrawals/losses to followup: NA Age: Mean (SD): 54.8 ± 9.6 (valsartan), 55.4 ± 10.1 (lisinopril) **Sex (n [%]):** Female: 3808 (57.3%) valsartan 8850 (51.1%) lisinopril Male: 2837 (42.7%) valsartan 8470 (48.9%) lisinopril Race/ethnicity (n [%]): NR **Baseline blood pressure:** NR **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** Using Deyo-Charlson index Mean: Valsartan 0 ± 0.8 Lisinopril 0 ± 0.9 Anemia: Valsartan: 239 (3.6%) Lisinopril: 600 (3.5%) Atrial fibrillation or flutter: Valsartan: 35 (0.5%) Lisinopril: 123 (0.7%) Coronary heart disease: Valsartan: 181 (2.7%) Lisinopril: 455 (2.6%)	**3) Mortality:** None **4) Morbidity:** In multivariate analysis, valsartan was associated with a reduced risk of a major cardiovascular or renal event compared with lisinopril although this finding was not statistically significant (HR, 0.89; 95% CI 0.74–1.07; P = 0.1987) Cardiovascular or renal event: Valsartan: 162 (2.4%) Lisinopril: 632 (3.6%) HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.77 (0.65–0.92) Multivariate analysis: 0.89 (0.74–1.07) Cardiovascular event: Valsartan: 137 (2.1%) Lisinopril: 513 (3.0%) HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.81 (0.67–0.97) Multivariate analysis: 0.92 (0.75–1.13) Myocardial infarction: Valsartan: 33 (0.5%) Lisinopril: 103 (0.6%) HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.98 (0.66–1.45) Multivariate analysis: 1.15 (0.75–1.74) Stroke: Valsartan: 31 (0.5%) Lisinopril: 90 (0.5%) HR (95% CI) valsartan vs. lisinopril (univariate analysis): 1.10 (0.73–1.66) Multivariate analysis: 1.27 (0.82–1.96)	Overall rating: Fair Comments: None **Applicability:** - Retrospective analysis limited in ability to overcome selection bias - Does not describe BP or safety/adverse events - Does not describe persistence - Followup time is unclear

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Heart failure:	
		Cerebrovascular disease:	Valsartan: 56 (0.8%)	
		Valsartan: 25 (0.4%)	Lisinopril: 289 (1.7%)	
		Lisinopril: 104 (0.6%)	HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.58 (0.44–0.78)	
		Diabetes:	Multivariate analysis: 0.69 (0.51–0.93)	
		Valsartan: 659 (9.9%)		
		Lisinopril: 3052 (17.6%)	Ventricular arrhythmias:	
			Valsartan: 11 (0.2%)	
		Hypercholesterolemia:	Lisinopril: 35 (0.2%)	
		Valsartan: 1923 (28.9%)	HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.97 (0.49–1.91)	
		Lisinopril: 5340 (30.8%)	Multivariate analysis: 0.81 (0.39–1.69)	
		Obesity:		
		Valsartan: 151 (2.3%)	Cardiac arrest:	
		Lisinopril: 467 (2.7%)	Valsartan: 4 (0.1%)	
			Lisinopril: 8 (0.0%)	
		Peripheral arterial disease:	HR (95% CI) valsartan vs. lisinopril (univariate analysis): 1.66 (0.50–5.56)	
		Valsartan: 26 (0.4%)	Multivariate analysis: 1.95 (0.47–8.08)	
		Lisinopril: 100 (0.6%)		
		Proteinuria:	Revascularization:	
		Valsartan: 16 (0.2%)	Valsartan: 46 (0.7%)	
		Lisinopril: 57 (0.3%)	Lisinopril: 148 (0.9%)	
			HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.94 (0.67–1.31)	
		Renal disease:	Multivariate analysis: 1.13 (0.80–1.61)	
		Valsartan: 32 (0.5%)		
		Lisinopril: 85 (0.5%)		
			CABG:	
		Valvular heart disease:	Valsartan: 15 (0.2%)	
		Valsartan: 8 (0.1%)	Lisinopril: 55 (0.3%)	
		Lisinopril: 25 (0.1%)	HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.84 (0.48–1.50)	
		Recruitment setting:	Multivariate analysis: 1.12 (0.62–2.05)	
		Pharmetrics Patient Centric Database		
			PCI:	
			Valsartan: 33 (0.5%)	
		Inclusion criteria: All persons in the database with two or more outpatient prescriptions for	Lisinopril: 97 (0.6%)	
			HR (95% CI) valsartan vs. lisinopril (univariate analysis): 1.02 (0.68–1.51)	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		valsartan, lisinopril, or extended-release metoprolol and two or more prior claims with a diagnosis of hypertension Exclusion criteria: - History of major cardiovascular or renal events (diagnosis of MI, stroke, heart failure, ventricular arrhythmias, or cardiac arrest; coronary revascularization procedure; diagnosis of renal failure; or dialysis or kidney transplantation) - Use of other antihypertensive medications except diuretics during the 12 months before treatment with valsartan, lisinopril, or extended-release metoprolol	Multivariate analysis: 1.15 (0.76–1.75) Renal event: Valsartan: 33 (0.5%) Lisinopril: 170 (1.0%) HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.60 (0.42–0.88) Multivariate analysis: 0.73 (0.49–1.08) Chronic renal failure: Valsartan: 30 (0.5%) Lisinopril: 155 (0.9%) HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.60 (0.41–0.90) Multivariate analysis: 0.70 (0.46–1.07) Dialysis: Valsartan: 4 (0.1%) Lisinopril: 29 (0.2%) HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.46 (0.16–1.30) Multivariate analysis: 0.73 (0.25–2.15) Kidney transplant: Valsartan: 0 (0.0%) Lisinopril: 0 (0.0%) HR (95% CI) valsartan vs. lisinopril (univariate analysis): NA Multivariate analysis: NA Unstable angina: Valsartan: 49 (0.7%) Lisinopril: 133 (0.8%) HR (95% CI) valsartan vs. lisinopril (univariate analysis): 1.12 (0.80–1.55) Multivariate analysis: 1.08 (0.76–1.53) Development of diabetes: Valsartan: 189 (3.2%) Lisinopril: 583 (4.1%)	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.86 (0.73–1.02) Multivariate analysis: 0.81 (0.68–0.96) Development of renal disease: Valsartan: 19 (0.3%) Lisinopril: 103 (0.6%) HR (95% CI) valsartan vs. lisinopril (univariate analysis): 0.54 (0.33–0.88) Multivariate analysis: 0.87 (0.52–1.46) **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Derosa, Cicero, Ciccarelli, et al., 2003 **#1574**	Geographical location: Pavia, Italy Study dates: NR Funding source: NR Interventions: - Perindopril 4 mg (n = 49) - Candesartan 16 mg (n = 47)	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 96 - Began treatment: 96 - Completed treatment: NR - Withdrawals/losses to followup: NR Age:	**1) Blood pressure:** Mean change (± SD) in BP from baseline to 12 mo: <u>Perindopril</u> <u>Candesartan</u> SBP -13 ± 4.5 -12 ± 4.1 DBP -11 ± 3.6* -8 ± 2.9 * p < 0.05, perindopril vs. candesartan; no other between-group comparisons	**General comments:** - Probably underpowered study Quality assessment: Overall rating: Good **Applicability:** - Very early diabetes with mild hypertension - Patients in academic medical

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Mean (SD): 54 median: NR Range: NR **Sex (n [%]):** Female: 49 (51%) Male: 47 (49%) Race/ethnicity (n [%]): NR, but presumably 100% Caucasian **Baseline blood pressure:** Trough seated BP measured 3 times at 1-min intervals after patient rested 10 min using a standard mercury sphygmomanometer (Erkameter 3000); average of 3 readings used Perindopril / Candesartan SBP 147 ± 6 / 148 ± 6 DBP 94 ± 4 / 93 ± 5 **Concurrent medications (n [%]):** Glibenclamide: 43% Glipizide: 30% Gliclazide: 28% **Comorbidities (n [%]):** NR **Recruitment setting:** Department of Internal Medicine and Therapeutics at a single university hospital	statistically significant 1-mo, 6-mo, 1-mo posttreatment followup data also reported **2) Rate of use of a single antihypertensive agent for BP control:** NA (no additional agents allowed) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Any AE: Perindopril: 5/49 (10%) Candesartan: 3/47 (6%) No serious AEs. No withdrawals due to AEs. **6) Specific adverse events:** Perindopril (n = 49): 2 (4%) cough, 4 (8%) abnormal taste, 1 (2%) epigastric discomfort Candesartan (n = 47): 1 (2%) headache, 2 (4%) dizziness, 1 (2%) nausea **7) Persistence/adherence:** NR **8) Lipid levels:** Values are mean ± SD: Perindopril / Candesartan LDL baseline: 120 ± 18 / 125 ± 15 LDL change 12 mo: -14 ± 7.4* / -4 ± 1.8 HDL baseline: 43 ± 4 / 40 ± 5	center in Italy - Probably underpowered to detect true differences between the groups

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results			Comments/ quality/applicability
		Inclusion criteria: - Type 2 diabetes diagnosed < 6 mo before - Mild hypertension (DBP 90-105 without meds) - Non-smokers - Adequate glycemic control (HbA1c < 7.5%) with diet or oral hypoglycemic drugs - Not on hypocholesterolemic drugs - No retinopathy, neuropathy, or nephropathy Exclusion criteria: - Secondary hypertension - Malignant hypertension - Unstable angina - MI within 6 months - Liver disease - Renal disease - Contraindication to ACEI or ARB - Already receiving ACEI or ARB	HDL change 12 mo TG baseline TG change 12 mo * p < 0.05, perindopril vs. candesartan 6-mo and 1-mo posttreatment followup data also reported **9) Progression to type 2 diabetes:** All already have type 2 diabetes **10) Markers of carbohydrate metabolism/diabetes control:** Values are mean ± SD: HbA1c baseline HbA1c change 12 mo Fasting glucose baseline Fasting glucose 1 yr * p < 0.05, perindopril vs. candesartan 6-mo and 1-mo posttreatment followup data also reported **11) LV mass/function:** NR **12) Creatinine/GFR:** NR	-2 ± 0.5 160 ± 18 -22 ± 11.6 Perindopril 6.4 ± 0.9 -0.2 ± 0.1 155 ± 15 -15 ± 4*	+2 ± 0.4 149 ± 10 +2 ± 0.8 Candesartan 6.5 ± 1.1 -0.2 ± 0.1 160 ± 13 -8 ± 2	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			13) Proteinuria: Values are mean ± SD: Perindopril / Candesartan AER/24 hr baseline: 17 (10) / 18 (11) AER/24 hr change 12 mo: -8 ± 3.6 / -8 ± 4.1 6-mo and 1-mo posttreatment followup data also reported	
Deyneli, Yavus, Velioglu, et al., 2006 **#1431**	Geographical location: Istanbul, Turkey Study dates: NR Funding source: Supported by a grant from the Turkish Diabetes Foundation, Istanbul, Turkey Interventions: 6-week titration phase of either: - Enalapril 5-20 mg/day (n = 12) - Losartan 50-100 mg/day (n = 12) targeting BP < 130/80 mm Hg Followed by 24-week maintenance phase Were additional anti-hypertension medications allowed: NR Study design:	Number of patients: N = 24 - Screened for inclusion: NR - Eligible for inclusion: 28 - Randomized: 26 - Began treatment: 26 - Completed treatment: 24 - Withdrawals/losses to followup: 1 enalapril (cough/dizziness) 1 losartan (non-compliant) Age: Mean (SD): 52.4 ± 6.0 **Sex (n [%]):** Female: 18 (75%) Male: 6 (25%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** 3 seated recordings after 10 min rest: Enalapril: 144.1/89.5 mmHg (18.8/4.5)	**1) Blood pressure:** Post-treatment seated BP: Enalapril: 125.0/76.2 mmHg (15.6/7.1) Losartan: 122.5/75.4 mmHg (18.3/4.5) No significant between-group difference **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** See specific adverse events **6) Specific adverse events:** 1 patient in enalapril had cough/dizziness. No reported AEs for losartan. **7) Persistence/adherence:** 1 pt in losartan withdrawn for non-compliance	**General comments:** Primary outcomes are biochemical urine markers Quality assessment: Overall rating: Fair Comments: None **Applicability:** Not clear if other antihypertensive meds allowed during treatment phase

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: Yes Baseline/run-in period: NA Duration of treatment: 6 months (6 weeks titration and 24 weeks maintenance) Duration of post-treatment followup: NR	Losartan: 142.5/90.0 mmHg (18.6/6.7) **Concurrent non-hypertension medications (n [%]):** NR 22/24 on oral antidiabetic meds and 2/24 on insulin **Comorbidities (n [%]):** All patients had diabetes **Recruitment setting:** University endocrine and internal medicine clinics Inclusion criteria: Male and female patients attending Marmara University Hospital Endocrine and Internal Medicine outpatient clinics with Type 2 DM diagnosed after the age of 30, with mild-to-moderate essential HTN and microalbuminuria. All patients were hypertensive for at least 6 months according to hospital records and none were on antihypertensive treatment. Exclusion criteria: - Secondary HTN - History of malignant HTN, MI, cerebrovascular disease, heart failure, treatment with anti-aggregants, steroids, or other drugs that might effect BP - Serum creatinine > 200 µmol/L - Urinary tract infection and other systemic disorders	**8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** Baseline GFR (creatinine clearance mL/min): Enalapril: 102.6 ± 22 Losartan: 115.9 ± 23 6 months Enalapril: 114.5 ± 30 Losartan: 111.6 ± 28 Statistical testing not reported. **13) Proteinuria:** Urine albumin excretion (mg/day): Enalapril: 83.5 ± 51 at baseline 17.5 ± 7.4 at 6months Losartan: 80.1 ± 52 at baseline 19.3 ± 8.4 at 6months No significant between-group difference	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Duprez, Munger, Botha, et al., 2010 (Epub 2009 Dec 24) **#2112** AGELESS trial	Geographical location: 100 centers in the US Study dates: NR Funding source: Funded by Novartis Pharma AG, Basel, Switzerland. Novartis was represented on the trial steering committee in the study design, analysis, and interpretation of data. The sponsor provided study drug preparations. Editorial assistance was provided by Complete Healthcare Communications Inc. (Chadds Ford, PA, USA) and supported by Novartis Pharmaceuticals Corporation. Interventions: - Aliskiren 150 mg/d, with increase to 300 mg/d at 4 or 8 weeks if sitting SBP ≥ 140 (n = 457) - Ramipril 5 mg/d, with increase to 10 mg/d at 4 or 8 weeks if sitting SBP ≥ 140 (n = 444) Were additional anti-hypertension medications allowed: Yes If Yes to above, was this done: Per protocol. HCTZ 12.5 mg/d added in either study arm at or after 12 weeks if sitting SBP ≥ 140. HCTZ increased to 25 mg/d at or after 16 weeks if sitting SBP	Number of patients: N = 901 - Screened for inclusion: NR - Eligible for inclusion: 1325 - Randomized: 901 - Began treatment: NR - Completed treatment: 680 (75%) - Withdrawals/losses to followup: 221 (25%). Age: Mean (SD): All 72.1 ± 5.6 Aliskiren 72.0 ± 5.6 Ramipril 72.2 ± 5.6 Range: ≥ 65 (32.5% were ≥ 75) **Sex (n [%]):** Female: 472 (52.4%) Male: 429 (47.6%) Race/ethnicity (n [%]): White 767 (85.1%) Black 72 (8.0%) Asian/other 62 (6.9%) **Baseline blood pressure:** Sitting and standing BP 24 ± 3 h after dose, with standard mercury sphygmomanometer and appropriate cuff size at baseline and weeks 2, 4, 8, 12, 16, 22, 28, and 36. Sitting BP was measured three times after the patient had been sitting for 5 min, with back supported and both feet placed on the floor. Mean sitting SBP, mm Hg ± SD (range): - Aliskiren: 156.5 ± 10.9 (137-	**1) Blood pressure:** Primary endpoint: change in SBP from baseline to week 12. <u>Mean sitting SBP, mm Hg ± SD</u> At week 12: - Aliskiren: Mean sitting SBP: 142.9 ± 18.0 Change: -14 ± 0.8 - Ramipril: Mean sitting SBP: 145.3 ± 16.1 Change: -11.6 ± 0.8 - Change between treatments: -2.3 mm Hg (95% CI, -4.3 to -0.3) Conclusion: "Aliskiren monotherapy showed statistically non-inferior ($p < 0.001$) and statistically superior ($p = 0.02$) reduction in mean sitting SBP compared with ramipril therapy." At week 22: - Aliskiren: 137.0 ± 17.8 Change: -19.6 ± 0.8 - Ramipril: 139.6 ± 16.8 Change: -17.3 ± 0.8 - Change between treatments: -2.4 mm Hg (95% CI, -4.5 to -0.3; $p = 0.03$) At week 36: - Aliskiren: 136.5 ± 17.3 Change: -20 ± 0.8 - Ramipril: 138.5 ± 16.9 Change: -18.1 ± 0.8 - Change between treatments: -1.9 mm Hg (95% CI, -4.0 to 0.2; $p = 0.07$) <u>Mean sitting DBP</u> At week 12: - Aliskiren: 80.7 ± 10.7	**General comments:** - Well-designed and well-reported study - Industry sponsor was involved in data analysis, interpretation, and authorship - Last observation carried forward was used to impute missing values in patients who discontinued before week 12 Quality assessment: Overall rating: Good **Applicability:** Good applicability. Good study design, appropriately powered, good blinding, and good reporting of methods and results. Insufficient data reported for recruitment and screening to know whether the sample population is representative of the larger population of patients with essential HTN in the U.S.

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	≥ 140. Amlodipine 5 mg/d added at or after 22 weeks if needed, and increased to 10 mg/d at 28 weeks if needed. Study design: RCT, parallel-group, double-blind, active-controlled, optional-titration Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: Yes Baseline/run-in period: 1 to 2 weeks of discontinuation of anti-hypertensive medications prior to randomization Duration of treatment: 36 weeks Duration of post-treatment followup: None. Last assessment after 36 weeks of treatment.	190) - Ramipril: 156.6 ± 10.6 (140-181) Mean sitting DBP, mm Hg ± SD (range): - Aliskiren: 85.5 ± 9.5 (51-109) - Ramipril: 78.4 ± 19.0 (60-107) **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** Diabetes: All: 20.6% - Aliskiren: 99 (21.7) - Ramipril: 87 (19.6) Obesity: All: 40.2% - Aliskiren: 183 (40.0) - Ramipril: 179 (40.3) **Recruitment setting:** Patients with essential hypertension recruited from 100 center in the US Per protocol, patients with SBP ≥ 180 or DBP ≥ 110 at any time, including run-in period, were withdrawn from study and appropriate therapy was instituted. Inclusion criteria: Men and women, age ≥ 65, with essential HTN (mean sitting SBP ≥ 140 to ≤ 180 mmHg and mean sitting DBP < 110mmHg) Exclusion criteria:	Change: -5.1 ± 0.4 - Ramipril: 82.5 ± 9.6 Change: -3.6 ± 0.4 - Change between treatments: -1.5 mm Hg (95% CI, -2.6 to -0.5; p < 0.01) At week 22: - Aliskiren: 77.8 ± 10.4 Change: -8.2 ± 0.4 - Ramipril: 78.9 ± 10.3 Change: -7.3 ± 0.4 - Change between treatments: -0.8 mm Hg (95% CI, -2.0 to 0.3; p = 0.14) At week 36: - Aliskiren: 77.6 ± 9.9 Change: -8.2 ± 0.5 - Ramipril: 79.1 ± 9.8 Change: -7.0 ± 0.4 - Change between treatments: -1.2 mm Hg (95% CI, -2.3 to -0.1; p = 0.03) At week 12, a greater percentage of aliskiren patients (42%) achieved BP control than ramipril patients (33%). BP changes were similar for aliskiren and ramipril in the subgroup of patients with Stage 2 HTN. BP changes appeared similar for age < 75 patients vs. ≥ 75 patients in aliskiren and ramipril groups (p values not reported). BP changes appeared less for black patients vs. white patients for aliskiren, but greater for black patients vs. whites for ramipril (p values not reported). **2) Rate of use of a single antihypertensive agent for BP control:**	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- History of severe cardiovascular or cerebrovascular disease or other life-threatening medical conditions - Serum sodium or potassium < lower limit of normal or if serum potassium was ≥ 5.5 $mEql^{-1}$ - Evidence of severe renal impairment with an estimated GFR < 30 mL/min per 1.73m^2 as measured by the Modification of Diet in Renal Diseases formula - Heavy proteinuria (urinary albumin to creatinine ratio > 3500 mgg^{-1}) or evidence of the nephritic syndrome	Aliskiren: 42% Ramipril: 29% (statistical significance not reported) "A significantly greater percentage of patients receiving ramipril than aliskiren required additional HCTZ (56 vs. 46%; p < 0.01)." "Similarly, a greater percentage of patients receiving ramipril-based (16%) vs. aliskiren-based (12%) therapies required add-on therapy with both HCTZ and amlodipine by week 36 (p = 0.048)." **3) Mortality:** None **4) Morbidity:** NR **5) Safety:** Any AE: Aliskiren: 328/452 (72.6%) Ramipril: 336/444 (75.7%) Serious AEs: Aliskiren: 35/452 (7.7%) Ramipril: 27/444 (6.1%) **6) Specific adverse events:** The statistically significant differences were: Aliskiren Ramipril p value D/C due to AEs 32 (7.1) 51 (11.5) 0.023 Cough 19 (4.2) 59 (13.3) < 0.0001 **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			10) Markers of carbohydrate metabolism/diabetes control: NR **11) LV mass/function:** NR **12) Creatinine/GFR:** eGFR change from baseline to week 36 (mL/min per 1.73 m^2): - Aliskiren: -3.20 ± 11.22 - Ramipril: -3.94 ± 12.32 Number (%) or patients exceeding pre-specified thresholds at any time post-baseline in creatinine and BUN: <u>Creatinine (> 176.8 micromol/L):</u> - Aliskiren: 2 (0.5) - Ramipril: 1 (0.2) <u>BUN (> 14.28 mmol/L):</u> - Aliskiren: 5 (1.1) - Ramipril: 4 (0.9) **13) Proteinuria:** NR	
Eguchi, Kario, and Shimada, 2003 **#1575**	Geographical location: Tochigi, Japan Study dates: NR Funding source: NR Interventions: - Candesartan (4-12 mg) (n = 37) - Lisinopril (5-20 mg) (n = 36) Dose titration/co-interventions: Initially, all patients treated with candesartan (4-8 mg) or lisinopril (5-10 mg) (choice of dose not	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 73 - Began treatment: 73 - Completed treatment: NR - Withdrawals/losses to follow-up: NR; all 12 patients who experienced AEs were "excluded from the study" - Population analyzed = 61 Age: Mean (SD): 69.3 ± 7.4 Median: NR	**1) Blood pressure:** Mean seated trough BP at 12 wk: Candesartan (n = 61) Lisinopril (n = 61) SBP 148 ± 16 144 ± 18 DBP 79 ± 11 77 ± 9.8 No significant difference between groups (p-values NR) Other outcomes reported: 24-hr ABPM outcomes	**General comments:** - Meds taken before randomization (no clear run-in period described): ACEI 41% ARB 6.6% Diuretics 16% Calcium antagonist 64% None 6.6% Quality assessment: Overall rating: Poor Comments: - Protocol not clearly defined, blinding not reported, no washout

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	explained). Dosage of candesartan was then increased by 4 mg and dosage of lisinopril by 5-10 mg for 4 wk up to the maximum. If response not satisfactory (BP systolic < 140 and BP diastolic < 90) at 4-8 wk, then trichlormethazide 1-2 mg added. At 12 wk, patients crossed over to the alternative drug as monotherapy, with dose titration and addition of diuretic repeated as above. Study design: RCT, crossover Blinding: - Patients: NR - Providers: NR - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: 1-week "washout" after randomization Washout period(s): No washout between study periods Duration of treatment: 2 x 12-week treatment periods Duration of post-treatment followup: NA	Range: NR **Sex (n [%]):** Female: 57% Male: 43% Race/ethnicity (n [%]): NR **Baseline blood pressure:** Seated trough BP measured after patient seated for 5 min rest using a standard mercury sphygmomano-meter Mean baseline values for analyzed population (n = 61): DBP: 163 ± 17 SBP: 85 ± 11 **Concurrent medications (n [%]):** **Comorbidities (n [%]):** Diabetes 48% Smoker 23% **Recruitment setting:** Clinic office Inclusion criteria: - Ambulatory, asymptomatic older patients with > 3 visits in a 14- to 28-day period with mean SBP > 150 mm Hg or mean DBP > 90 on > 2 occasions Exclusion criteria: - Serum creatinine > 2.5 mg/dL - Major stroke, congestive heat failure, malignancy or other	**2) Rate of use of a single antihypertensive agent for BP control:** Trichlormethazide added per protocol: Candesartan: 79% Lisinopril: 80% p = NS **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Patients with AEs requiring their "exclusion" from analysis: Candesartan: 2 patients (2.7%; 1 dim vision and 1 facial edema) Lisinopril: 10 patients (13.7%; 9 cough, 2 fatigue) (numbers given here as reported) **6) Specific adverse events:** NR except AEs leading to withdrawal (see immediately above) **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	after period 1 of crossover, imbalance in treatment groups (apparently due to more patients discontinuing lisinopril and not continuing to period 2) - Of the 61 patients analyzed, 35 received candesartan first and 26 lisinopril first - Patients with AEs (n = 12) excluded from efficacy analysis **Applicability:** - Apparently limited to Japanese patients in a single clinic

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		severe concomitant disease - BP > 180/110 mm Hg on medication - Note: Patients with MI with preserved LV contractility and those with "minor" stroke were *not* excluded		
Elliott, 1999 **#1576** *and* **Gavras and Gavras, 1999** **#1583** *and* **Levine, 1999** **#1593** *and* **Argenziano and Trimarco, 1999** **#1557** *and*	Geographical location: North America, Europe, and South Africa Study dates: NR Funding source: SmithKline Beecham Pharma (Collegeville, PA; since merged with GlaxoSmithKline, now GSK) Interventions: - Enalapril 5 mg qd, with titration up to 20 mg qd (n = 264) - Eprosartan 200 mg bid, with titration up to 300 mg bid (n = 264) Both groups: HCTZ 12.5-25 mg qd added at 12 wk if DBP ≥ 90) Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes (titration/maint) - Assessors of outcomes: NR Was allocation concealment adequate?: NR	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 528 - Began treatment: NR - Completed treatment: 447 - Withdrawals/losses to followup: NR (≥ 16) Age: Mean (± SEM): 55.6 ± 0.7 Median: NR Range: 23-84 **Sex (n [%]):** Female: 56.5% Male: 43.5% Race/ethnicity (n [%]): Caucasian 456 (86%) Black 40 (8%) Asian 6 (1%) Other 26 (5%) **Baseline blood pressure (± SEM);** Sitting BP measured in triplicate "according to standard techniques" Enalapril Eprosartan	**1) Blood pressure:** Mean post-treatment BP values NR <u>Overall study population</u> Mean change in BP from baseline (at 26 wk): <u>Enalapril</u> <u>Eprosartan</u> Sit SBP -14.7 -15.5 mm Hg Sit DBP -11.9 -12.9 mm Hg Response rates (DBP < 90 or DBP < 100 and a reduction of ≥ 10 mm Hg from baseline): <u>Enalapril</u> <u>Eprosartan</u> 12 wk 62.6% 70.3% (p < 0.05) 26 wk 73.4% 81.7% (p < 0.02) <u>≥ 65 years subgroup</u> Mean change in BP from baseline (at 26 wk): <u>Enalapril</u> <u>Eprosartan</u> Sit SBP -15.3 ± 2.2 -18.9 ± 2.1 (NS) Sit DBP -12.2 ± 1.1 -13.9 ± 1.1 (NS) Response rates: <u>Enalapril</u> <u>Eprosartan</u>	**General comments:** - An analysis comparing the subgroups < 65 years and ≥ 65 years of age found that the elderly subpopulation "mirrored the response of the study as a whole" - An analysis of a subgroup of 40 black patients found that the black subpopulation "mirrored the response of the study as a whole" Quality assessment: Overall rating: Fair Comments: - Method of BP ascertainment not described - Uncertainty about number of withdrawals (enumerated those w/d for serious AE and cough; but not for any other causes, if any) - One report described 529 patients instead of 528; other minor discrepancies across reports **Applicability:** - No list of participating centers (described as multinational) - Poor description of subjects' comorbidities, although exclusion criteria suggest a comparatively healthy group

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Breeze, Rake, Donoghue, et al., 2001 **#1564**	Baseline/run-in period: 3- to 5-wk single-blind placebo run-in Duration of treatment: 26 wk: 18-wk titration period + 8-wk maintenance period Duration of post-treatment followup: None	SBP 156.2 ± 0.9 156.4 ± 0.9 DBP 101.2 ± 0.3 100.7 ± 0.3 Baseline values also reported for ≥ 65 years subgroup and black subgroup **Concurrent medications (n [%]):** NR; concomitant use of medications know to affect BP prohibited **Comorbidities (n [%]):** Current smoker: Enalapril: 31 (12%) Eprosartan: 36 (14%) See also Exclusion criteria, below **Recruitment setting:** NR Inclusion criteria: - Age ≥ 18 yr - Essential HTN (sitting DBP 95-114 mm Hg) Exclusion criteria: - Secondary forms of hypertension - Advanced hypertensive retinopathy - Sitting SBP > 200 mmHg - MI or CVA < 90 days - CHF or angina - Advanced AV conduction defects, ventricular	26 wk 48 (77.4%) 55 (87.3%) (NS) Black patient subgroup Mean change in BP from baseline (at 26 wk): Enalapril Eprosartan Sit SBP -10.5 ± 3.7 -18.8 ± 3.5 (NS) Sit DBP -9.6 ± 2.4 -10.5 ± 1.9 (NS) Response rates: Enalapril Eprosartan 12 wk 5 (26.3%) 11 (52.4%) (p < 0.05) 26 wk 8 (42.1%) 14 (66.7%) (p = 0.02) **2) Rate of use of a single antihypertensive agent for BP control:** Eprosartan group: HCTZ added in 81 patients Enalapril group: HCTZ added in 81 patients **3) Mortality:** One death in eprosartan group; judged to be unrelated **4) Morbidity:** One MI in eprosartan group, judged to be unrelated to treatment. The between-group differences in changes in Psychological General Well Being (PGWB) scores were -2.48 (95% CI -4.63 to -0.32) for the study end point and -0.79 (-2.72 to 1.15) for monotherapy end point.	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		tachyarrhythmias, bradycardia - Unstable DM - Clinically significant renal or hepatic disease - Other concurrent severe disease - Emphysema, chronic bronchitis, asthma with cough, URI < 2 wks	At monotherapy end point there were no significant differences between treatments (data not presented). **5) Safety:** Enalapril / Eprosartan Severe AE 32 (12.1%) / 24 (9.1%) Tx-related 16 (6.1%) / 10 (3.8%) Serious nonfatal 8 (3.0%) / 4 (1.5%) ≥ 1 AE 213 (80.7%) / 201 (76.1%) ≥ 65 years subgroup All AE 48 (77.4%) / 46 (73.0%) All Serious 7 (11.3%) / 4 (6.3%) Serious - w/d 1 / 1 Serious - no w/d 3 / 0 **6) Specific adverse events:** Enalapril / Eprosartan Definite cough 14 (5.4%) / 4 (1.5%) Cough (p = 0.01) 59 (22.3%) / 34 (12.9%) Pharyngitis 64 (24.2%) / 44 (16.7%) Headache 37 (14.0%) / 39 (14.8%) Rhinitis 43 (16.3%) / 33 (12.5%) URI 43 (16.3%) / 33 (12.5%)	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Myalgia

16 (6.1%)	25 (9.5%)

Dyspnea

17 (6.4%)	14 (5.3%)

Dizziness

21 (8.0%)	13 (4.9%)

Fatigue

18 (6.8%)	13 (4.9%)

*definite cough – persistent, non-productive (dry) cough assoc. with tx and not due to URI as judged by investigator

7) Persistence/adherence: NR

8) Lipid levels:

	Eprosartan		Enalapril	
	baseline	end	baseline	end
LDL-c	3.5±0.8	3.6±0.9	3.5±0.9	3.7±0.9
HDL-c	1.4±0.3	1.4±0.4	1.4±0.4	1.4±0.3
TG	1.6±1.0	1.6±1.1	1.6±1.0	1.7±1.1

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: "Neither eprosartan nor enalapril significantly affected … blood glucose" at any time point.

11) LV mass/function: NR

12) Creatinine/GFR: "The degree and direction of … renal function tests were comparable in both treatment groups."

13) Proteinuria: NR

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Erkens, Panneman, Klungel, et al., 2005 **#1577**	Geographical location: 25 medium-sized cities in The Netherlands Study dates: Included patients received treatment between 1997 and 2001 Funding source: Novartis Pharma, B.V. (The Netherlands) Interventions: Diuretics (n = 458) Beta-blockers (n = 471) CCBs (n = 455) ACEIs (n = 412) ARBs (n = 447) Study design: Retrospective cohort study Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: NA Baseline/run-in period: NA Duration of treatment: NR Duration of post-treatment followup: Patients followed for 15 mo after their index data	Number of patients: - Screened for inclusion: 48,234 - Eligible for inclusion: 2243 (after random selection of 500 per group and post-selection exclusions) - Randomized: NA - Began treatment: NA - Completed treatment: NA - Withdrawals/losses to followup: NA Age: Mean (SD): NR Median: NR Range: - 0-19: 1.6% - 20-39: 11.5% - 40-59: 42.6% - 60-79: 37.0% - ≥ 80: 7.4% **Sex (n [%]):** Female: 1276 (56.9%) Male: 967 (43.1%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** Antidiabetic drugs: 11.3% Lipid-lowering drugs: 9.4% Antiasthmatic drugs: 14.2% **Comorbidities (n [%]):** Prior CV hospitalizations: 8.2%	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** 1-yr persistence (defined as the % of patients who used a given drug for ≥ 270 days and had an additional drug dispensing in the 3 mo after the followup period): Diuretics: 33.0% Beta-blockers: 35.0% CCBs: 34.7% ACEIs: 59.7% ARBs: 62.0% Persistence increased with male sex, increas age, use of antidiabetic drugs, use of lipid-lowering drugs, and prior cardiovascular hospitalizations (all in univariable analyses) **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR	**General comments:** - High-quality administrative data in a population-based sample Quality assessment: Overall rating: Fair Comments: - Non-random allocation to drugs - No data on comparability of patients on ACEIs versus ARBs - Funded by pharmaceutical company **Applicability:** - Specific ACEIs and ARBs not identified

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Recruitment setting: **-** Data drawn from community-based database linking drug-dispensing records from pharmacies and hospital discharge records - Patients receive first antihypertensive prescription from GP (85%), internist (5.8%), cardiologist (4.0), or other (5.2%) Inclusion criteria: - From base cohort (n = 48,234), patients selected who: (1) did not use antihypertensive drugs in the year before the index date; (2) were registered in the database for ≥ 1 yr before and ≥ 15 mo after their first prescription for antihypertensive drugs; and (3) received at least two prescriptions for antihypertensive drugs - From this group, 500 per drug class randomly drawn for analysis Exclusion criteria: Patients using fixed combination drugs	**12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Fernandez-Campo, Grande, Diego, et al., 2009 **#72**	Geographical location: Salamanca, Spain Study dates: July 2004–Jan 2008 Funding source: European Commission Research Directorates General [grant number ERG-Mobility-11 #508782]; the Instituto de Salud Carlos III (Ministerio de Sanidad y Consumo) [grant numbers CP01/00094, P1041817]; the Junta de Castilla y León [grant numbers SA001/C05, SA029/A05]; and the Fundación de Investigación Médica Mutua Madrileña Interventions: - 13 patients with hypertension without diabetes treated with ARBs (600 mg/day eprosartan [n = 9], 50 mg/day losartan [n = 2] or 80 mg/day valsartan [n = 2]); - 19 patients with hypertension without diabetes treated with ACEI (either 20 mg/day enalapril [n = 12] or 2 mg/day trandolapril [n = 7]); - 23 patients with hypertension and diabetes treated with ARBs (600 mg/day eprosartan [n = 2], 50–100 mg/day losartan [n = 2], 80–160 mg/day valsartan [n = 18] or 150 mg/day irbesartan [n =	Number of patients: N = 81 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: 81 - Completed treatment: NR - Withdrawals/losses to followup: NR Age: Mean (SD): 62.15 ±4.41 **Sex (n [%]):** Female: 29 (35.8%) Male: 52 (64.2%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** SAP (mmHg): Patients with hypertension ARBs 151 ± 5 ACEIs 165 ± 3 Patients with hypertension and diabetes ARBs 174 ± 5 ACEIs 178 ± 7 DAP (mmHg) Patients with hypertension ARBs 93 ± 4 ACEIs 96 ± 2 Patients with hypertension and diabetes ARBs 93 ± 3 ACEIs 99 ± 5	**1) Blood pressure:** 3 months (means ± +/- SEM) [note not standard deviation] SAP (mmHg) Patients with hypertension ARBs 126 ± 5 ACEi 128 ± 2 Patients with hypertension and diabetes ARBs 156 ± 7 ACEi 157 ± 11 DAP (mmHg) Patients with hypertension ARBs 80 ± 3 ACEi 78 ± 2 Patients with hypertension and diabetes ARBs 85 ± 3 ACEi 89 ± 4 MAP (mmHg) Patients with hypertension ARBs 95 ± 3 ACEi 95 ± 2 Patients with hypertension and diabetes ARBs 109 ± 4 ACEi 111 ± 6 **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR	**General comments:** None Quality assessment: Overall rating: Poor Comments: No discussion of how patients were found, or how randomized to treatment **Applicability:** - Patients were not randomized - Does not provide information about adverse events

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	1]); - 9 patients with hypertension and diabetes treated with ACEI (20–40 mg/day enalapril [n = 4], 2 mg/day trandolapril [n = 3], 20 mg/day lisinopril [n = 1] or 10 mg/day imidapril [n = 1]). Were additional anti-hypertension medications allowed: No Study design: Other – non-randomized clinical trial Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: NA Baseline/run-in period: NA Duration of treatment: 3 months Duration of post-treatment followup: NA	MAP (mmHg) Patients with hypertension ARBs 112 ± 4 ACEIs 119 ± 2 Patients with hypertension and diabetes ARBs 120 ± 3 ACEIs 125 ± 5 **Concurrent non-hypertension medications (n [%]):** None **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: Newly diagnosed essential arterial HTN (BP 140/90 mmHg, or 130/80 mmHg in pts with DM) w/o or with diabetes (blood glucose > 125 mg/dl), mainly type 2 DM Exclusion criteria: - Previous antihypertensive treatment - Serious pathologies (other than HTN and DM) - Renal or hepatic failure Cardiac congestive insufficiency - Treatment with corticosteroids, non-steroid anti-inflammatory drugs and other potential HTN-inducing drugs - Heavy smoking - Alcoholism	**5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Fogari, Derosa,	Geographical location: Pavia, Italy	Number of patients: N = 246 - Screened for inclusion: 450	**1) Blood pressure:** There were substantial reductions in SBP	**General comments:** Patients who did not achieve BP

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Ferrari, et al., 2008 **#1221**	Study dates: Sep 1, 2004 – Aug 30, 2007 Funding source: NR Interventions: - Ramipril (5 mg, titrated to 7.5 mg titrated to 10 mg, 124 patients) - Valsartan (160 mg titrated to 240 mg titrated to 320mg, 122 patients) Titrated after 4 weeks and 8 weeks of treatment to achieve a target BP of < 140/90 mmHg Study also included amlodipine group (n = 123) Were additional anti-hypertension medications allowed: NR (possibly allowed as long as not "AT1R blockers, ACEIs, or antiarrythmic agents") If Yes to above, was this done: NA (certainly not per protocol) Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: NR	- Eligible for inclusion: 369 - Randomized: 369 - Began treatment: 246 (note additional 123 randomized to amlodipine but results not relevant here) - Completed treatment: 192 - Withdrawals/losses to followup: 54 Age: Mean (SD): 65 ± 7.5 **Sex (n [%]):** Female: 132 (53.7%) Male: 114 (46.3%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** BP measurements were obtained from each patient in the seated position using a standard mercury sphygmomanometer (Korotkoff I and V). Measurements were taken in the morning before daily drug intake (i.e., 24 h after dosing) and after the subject had rested 10 min in a quiet room. Three successive BP readings were taken at 1-min intervals and averaged. SBP (mm Hg): Ramipril 152 ± 7 Valsartan 153 ± 7 DBP (mm Hg): Ramipril 95 ± 2 Valsartan 95 ± 3	and DBP values in the two treatment groups. At the end of follow-up, SBP was reduced by 15.7 mm Hg (P < 0.001 vs. baseline) in the valsartan group, and by 15.8 mm Hg in the ramipril group (P < 0.001 vs. baseline), with no significant difference between treatments. Corresponding changes for DBP were 12.1, 12.2 mm Hg (P < 0.001 vs. baseline), respectively, again without any significant difference between treatments. **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** See AE findings below, as well as safety/specific adverse events **5) Safety:** Total AEs requiring the discontinuation of treatment occurred in 5 patients in the ramipril group, and 1 patient in the valsartan group. In the ramipril group, 1 patient had an atrial flutter and underwent radiofrequency ablation, and 4 patients discontinued because of an intolerable and unproductive cough. In the valsartan group, 1 patient discontinued because of hypotension. **6) Specific adverse events:** See immediately above **7) Persistence/adherence:** Ramipril: Discontinued AE n = 5 Uncontrolled BP n = 22	control were excluded from analyses Quality assessment: Overall rating: Good **Applicability:** No limitations noted

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Other n = 4	
	Baseline/run-in period: 2-week placebo period	**Concurrent non-hypertension medications (n [%]):** NR	Valsartan: Discontinued AE n = 1	
	Duration of treatment: 1 year	**Comorbidities (n [%]):** All patients had history of recent AF episode	Uncontrolled BP n = 20 Other n = 2	
	Duration of post-treatment followup: NA	Ramipril Valsartan LVH 14 (11.3) 16 (13.1)	**8) Lipid levels:** NR	
			9) Progression to type 2 diabetes: NR	
		Recruitment setting: Hypertension referral center	**10) Markers of carbohydrate metabolism/diabetes control:** NR	
		Inclusion criteria: Outpatients of either sex, with mild essential HTN, in sinus rhythm but with at least two ECG-documented episodes of symptomatic AF in the previous 6 months, and without any antiarrythmic treatment	**11) LV mass/function:** NR	
			12) Creatinine/GFR: NR	
			13) Proteinuria: NR	
			14) Atrial fibrillation: Intention-to-treat analysis	
		Exclusion criteria: - Treatment with AT1R blockers, ACEIs, or antiarrythmic agents, cardioversion within the last 8 weeks - Secondary HTN - MI or stroke in the preceding 6 months - CHF, coronary heart disease, valvular disease, DM, a left atrium size > 45 mm, need to continue the use of digitalis, or cardiac surgery during the previous 6 months - Significant thyroid, pulmonary renal of hepatic disease - Pregnancy or fertile female - Known hypersensitivity or	Recurrence of atrial fibrillation at 12 weeks after randomization: Ramipril 11 Valsartan 5 Recurrences of atrial fibrillation at 1 year after randomization Ramipril 26 Valsartan 16* Days to recurrence, median ± SD (range) Ramipril 126 ± 79 (44–344) Valsartan 160 ± 94 (69–350) * P < 0.05 vs. ramipril. At the 12-week follow-up visit (end of	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		contraindications to study medications	titration period), 33 patients had a recurrence of atrial fibrillation: by intention-to-treat analysis, the occurrence rate was significantly lower in the valsartan group (5 patients) than in the amlodipine group (17 patients). Kaplan–Meier analysis demonstrated a 12-week probability of 95% for maintaining sinus rhythm in patients who received valsartan compared with 91% in patients who received ramipril and 85% in patients who received amlodipine (P = 0.02). At the end of the follow-up (median 258 days [range 29–360]), 46 (47.4%) patients undergoing treatment with amlodipine had a recurrence of atrial fibrillation, as did 26 (27.9%) patients undergoing treatment with ramipril (P < 0.01 vs. amlodipine) and 16 (16.1%) patients undergoing treatment with valsartan (P < 0.01 vs. amlodipine and P < 0.05 vs. ramipril). Figure 2 in the manuscript shows the Kaplan–Meyer AF recurrence-free survival analysis, which demonstrated a significant reduction in AF recurrence in the valsartan group (P = 0.005 log-rank test) as well as in the ramipril group (P = 0.021 log-rank test) when compared to the amlodipine group, but also in the valsartan group (P = 0.045 log-rank test) when compared to the ramipril group.	
Fogari, Mugellini, Zoppi, et al., 2002 **#1578**	Geographical location: Pavia, Italy Study dates: NR Funding source: NR Interventions: - Perindopril 4 mg daily (n = 42)	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 85 - Began treatment: 85 - Completed treatment: 82 - Withdrawals/losses to followup: 3 (2 due to AEs, 1 failure to appear at visit)	**1) Blood pressure:** Mean trough seated BP at 12 wk: Perindopril / Losartan SBP 146 ± 10 / 147 ± 11 DBP 87 ± 5 / 88 ± 5 p = 0.001 for all pre-/post- comparisons p = NS for between-treatment comparisons	**General comments:** None Quality assessment: Overall rating: Fair Comments: - Numbers screened and eligible NR

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Losartan 50 mg daily (n = 43) No dose titration; no co-interventions specified Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: 4-wk placebo run-in Duration of treatment: 12 wk Duration of post-treatment followup: NA	Age: Mean (SD): 58.4 (8.0) Median: NR Range: 46-64 **Sex (n [%]):** Female: 40 (47%) Male: 45 (53%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Trough seated BP assessed using a standard mercury sphygmanometer; 3 readings taken at 1-min intervals after patient rested 10 min; average of 3 readings used Perindopril / Losartan SBP 163.2 ± 12.9 / 162.9 ± 12.6 DBP 102.8 ± 6.1 / 102.7 ± 5.9 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** 100% type 2 diabetes **Recruitment setting:** NR Inclusion criteria: **-** Adult men and women - Documented mild-to-moderate essential HTN (DBP 90-110) - Concomitant type 2 diabetes in	Mean change in BP at 12 wk: Perindopril / Losartan SBP -16 / -15 DBP -15 / -14 p < 0.001 for all pre-/post- comparisons p = NS for between-treatment comparisons **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** 2 withdrawals due to AEs – treatment group(s) not specified **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** Mean HDL (mg/dL): Baseline / 12 wk / p-value Perindopril 44 ± 5 / 46 ± 6 NS Losartan 44 ± 5 / 44 ± 6 NS Mean total cholesterol (mg/dL): Baseline / 12 wk / p-value Perindopril	- AEs not well reported - Details of dose titration and concomitant med use (if any) not given **Applicability:** - 100% of study population also has type 2 diabetes - Racial diversity not described (? 100% Caucasian) - Recruitment setting(s) not described - 44 patients never treated before for hypertension

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results			Comments/ quality/applicability
		stable metabolic control with diet and oral hypoglycemic agents Exclusion criteria: - Secondary HTN - Previous or active ischemic heart disease - Serum creatinine > 1.5 mg/dL - Chronic liver disease - Obesity (BMI >28) - Pregnancy	197 ± 23 Losartan 191 ± 20 Mean triglycerides (mg/dL): Baseline Perindopril 142 ± 49 Losartan 145 ± 50 **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** Mean FBG (mg/dL): Baseline Perindopril 112 ± 7.3 Losartan 113 ± 7.5 Mean HbA1c (%): Baseline Perindopril 7.2 ± 1.9 Losartan 6.9 ± 2.0 **11) LV mass/function:** NR **12) Creatinine/GFR:** Mean serum creatinine (mg/dL): Baseline Perindopril 1.1 ± 0.4 Losartan 1.1 ± 0.5 **13) Proteinuria:** NR	186 ± 19 188 ± 19 12 wk 127 ± 44 140 ± 48 12 wk 107 ± 6.9 111 ± 7.0 12 wk 7.1 ± 1.7 7.0 ± 1.8 12 wk 1.1 ± 0.4 1.1 ± 0.4	NS NS p-value NS NS p-value NS NS p-value NS NS	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Fogari, Mugellini, Zoppi, et al., 2004 **#1579**	Geographical location: NR (authors based in Pavia, Italy) Study dates: NR Funding source: NR Interventions: - Valsartan 160 mg (n = 75) - Enalapril 20 mg (n = 75) No dose titration; no co-interventions permitted Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: Yes Was allocation concealment adequate?: NR Baseline/run-in period: 2-wk run-in; previous anti-HTN treatment withdrawn Duration of treatment: 16 wk Duration of post-treatment followup: NA	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 150 - Began treatment: 150 - Completed treatment: 140 - Withdrawals/losses to followup: 6 (2 due to lack of compliance, 3 due to missed clinic visit, and 1 due to concomitant illness) Age: Mean (SD): 70.3 ± 5.7 Median: NR Range: NR **Sex (n [%]):** Female: 79/144 (54%) Male: 65/144 (46%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Trough seated BP measured using a standard mercury sphygmomano-meter after patient rested in sitting position for 5 min; mean of 3 measurement taken at 2-min intervals used Valsartan / Enalapril SBP 165.9 ± 7.3 / 165.8 ± 6.8 DBP 100.8 ± 3.7 / 100.9 ± 3.9 **Concurrent medications (n [%]):**	**1) Blood pressure:** Trough seated BP at 16 wk: Valsartan (n = 73) / Enalapril (n = 71) / P-value SBP 147.3 ± 7.3 / 150.2 ± 8.0 < 0.01 DBP 87.1 ± 4.7 / 90.4 ± 5.0 < 0.001 BP normalized at 16 wk (DBP < 90 mm Hg): Valsartan: 60.2% Enalapril: 52.1% p = NS **2) Rate of use of a single antihypertensive agent for BP control:** See immediately above on % of patients who normalized at 16 wk on monotherapy. **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Any AE: Valsartan: 5 (6.8%) Enalapril: 9 (12.6%) No serious AEs that were considered to be drug-related **6) Specific adverse events:** Cough n = 4 enalapril and n = 1 valsartan HA V = 2 and E = 2 Nausea V = 1 E = 2 **7) Persistence/adherence:** "Patient	**General comments:** None Quality assessment: Overall rating: Fair Comments: - Not everyone blinded - No titration for increase blood pressure **Applicability:** - Many comorbidities excluded in this elderly population and again comorbidities not presented - No data on race/ethnicity of subjects

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		NR; concomitant drugs with antihypertensive properties prohibited **Comorbidities (n [%]):** NR **Recruitment setting:** Outpatient clinics Inclusion criteria: Outpatients 61-80 years of age with mild-moderate hypertension (DBP ≥ 95 and ≤ 110) at end of 2-wk run-in Exclusion criteria: - Secondary arterial hypertension, sitting systolic blood pressure > 200, malignant hypertension, K_W retinopathy III or IV, a hx of HTN encephalopathy - CVA within 6 months, previous or current heart failure, MI within 6 months, angina, valvulopathy or relevant arrythmia - Hepatic or renal dysfunction - Clinical hypo or hyperthyroidism - Known hypersensitivity to ACEI or ARB	compliance to both treatments was satisfactory" (no quantitative data reported) **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Fogari, Mugellini, Zoppi, et al., 2006 **#283**	Geographical location: Pavia, Italy Study dates: NR Funding source: NR Interventions: - Telmisartan 80 mg/HCTZ 12.5	Number of patients: N = 160 - Screened for inclusion: NR - Eligible for inclusion: 160 - Randomized: 160 - Began treatment: 160 - Completed treatment: 147 - Withdrawals/losses to followup: 13	**1) Blood pressure:** Mean values of ambulatory BP (SBP ± SD/DBP ± SD) during treatment with telmisartan/HCTZ and lisinopril/HCTZ: *24-hour ambulatory BP:* Baseline: Telmisartan/HCTZ: 151.5 ± 9.9 Lisinopril/HCTZ: 151.3 ± 10.2	**General comments:** Study focuses on cognitive function in elderly hypertensive patients Quality assessment: Overall rating: Fair Comments: None

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	mg (n = 80) - Lisinopril 20 mg/HCTZ 12.5 mg (n = 80) Were additional anti-hypertension medications allowed: No Study design: RCT, parallel-group {([prospective, open-label, blinded end point, parallel-group design [PROBE]) Blinding: - Patients: No - Providers: No - Assessors of outcomes: Yes Was allocation concealment adequate?: NR Baseline/run-in period: 2-weeks Duration of treatment: 24 weeks Duration of post-treatment followup: NA	Age: Mean (SD): 67.6 ± 4.5 Range: 61 to 75 **Sex (n [%]):** Female: 84 (52.5%) Male: 76 (47.5%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Baseline readings for ambulatory blood pressure readings are listed in the results **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: Sitting DBP ≥ 95 and < 110 mmHg and sitting SBP > 140 mmHg Exclusion criteria: - Secondary HTN - MI or cerebrovascular accident within the preceding 6 months - Clinically significant valvular heart disease, heart failure, renal or hepatic insufficiency - Known hypersensitivity to the drugs used in the study	12 weeks: Telmisartan/HCTZ: 132.1 ± 5.0 Lisinopril/HCTZ: 133.6 ± 5.5 24 weeks: Telmisartan/HCTZ: 129.3 ± 5.2* Lisinopril/HCTZ: 131.7 ± 5.4 * P < 0.05 vs. lisinopril/HCTZ <u>*Daytime ambulatory BP:*</u> Baseline: Telmisartan/HCTZ: 155.8 ± 9.9 Lisinopril/HCTZ: 155.5 ± 10.2 12 weeks: Telmisartan/HCTZ: 136.0 ± 5.0* Lisinopril/HCTZ: 137.5 ± 5.5 24 weeks: Telmisartan/HCTZ: 133.1 ± 5.3* Lisinopril/HCTZ: 135.4 ± 5.4 * P < 0.05 vs. lisinopril/HCTZ <u>*Nigh time ambulatory BP:*</u> Baseline: Telmisartan/HCTZ: 138.7 ± 11.5 Lisinopril/HCTZ: 138.7 ± 11.6 12 weeks: Telmisartan/HCTZ: 120.4 ± 6.8 Lisinopril/HCTZ: 121.8 ± 7.4 24 weeks: Telmisartan/HCTZ: 117.4 ± 6.8* Lisinopril/HCTZ: 119.8 ± 7.2 * P < 0.05 vs. lisinopril/HCTZ **2) Rate of use of a single antihypertensive agent for BP control:**	**Applicability:** - Not enough description of patient recruitment

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Six patients reported one or more AEs; two (2.6%) treated with telmisartan (one headache, one dizziness) and four (5.5%) treated with lisinopril (2 cough, 1 dizziness, 1 gastric discomfort) **6) Specific adverse events:** See immediately above **7) Persistence/adherence:** Based on pill counting, 94% of prescribed tablets were taken during telmisartan therapy and 92% during lisinopril, indicating good treatment compliance **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Fogari, Zoppi, Preti, et al., 2001	Geographical location: Pavia, Italy Study dates: NR	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 89 - Began treatment: 89	**1) Blood pressure:** Mean trough seated BP at 12 wk: <u>Trandolapril</u> <u>Losartan</u> SBP 145.2 ± 10 145.5 ± 11	**General comments:** None Quality assessment: Overall rating: Fair

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
#1580	Funding source: NR Interventions: - Trandolapril 2 mg daily (n = 45) - Losartan 50 mg daily (n = 44) Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: 4-wk placebo run-in period Duration of treatment: 12 wk Duration of post-treatment followup: NA	- Completed treatment: 89 - Withdrawals/losses to followup: NA Age: Mean (SD): 55.5 (2) Median: NR Range: 51-60 **Sex (n [%]):** Female: 89 (100%) Male: 0 Race/ethnicity (n [%]): NR **Baseline blood pressure:** Seated trough BP measured using a standard mercury sphygmanometer; mean of 3 readings at 1-min intervals after 10 min rest Trandolapril / Losartan SBP 162.1 ± 12 / 160.6 ± 12 DBP 101.2 ± 5 / 100.5 ± 5 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: - Mild-moderate essential HTN (DBP 90-110 mm Hg - Postmenopausal women	DBP 88.1 ± 4 / 88.6 ± 5 p < 0.01 for all pre-/post- comparisons p = NS for between-treatment comparisons Mean change in BP at 12 wk: Trandolapril / Losartan SBP -17 / -15 DBP -13 / -12 p < 0.01 for all pre-/post- comparisons p = NS for between-treatment comparisons **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** Mean HDL (mg/dL): Baseline / 12 wk / p-value Trandolapril 50 ± 15 / 50 ± 16 / NS Losartan 49 ± 16 / 48 ± 17 / NS Mean total cholesterol (mg/dL): Baseline / 12 wk / p-value Trandolapril	Comments: - Numbers screened and eligible NR - AEs not well reported - Details of dose titration and concomitant med use (if any) not given **Applicability:** - 100% of study population post-menopausal women - Racial diversity not described (? 100% Caucasian) - Recruitment setting(s) not described

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		(defined by cessation of menses ≥ 1yr; confirmed by: (1) plasma FSH > 20 U/L; (2) FSH > LH levels; and (3) plasma 17-β-estradiol < 50 pmol/L) Exclusion criteria: - Hormone replacement therapy < 6 mo - Diabetes mellitus, obesity, smoking, MI, or stroke < 6 mo - History of breast cancer or thromboembolic disease - Major systemic diseases - Any condition that would require use of concomitant medications	231 ± 31 226 ± 29 NS Losartan 227 ± 33 224 ± 31 NS Mean triglycerides (mg/dL): <u>Baseline</u> <u>12 wk</u> <u>p-value</u> Trandolapril 128 ± 59 125 ± 57 NS Losartan 120 ± 51 123 ± 50 NS **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** Mean FBG (mg/dL): <u>Baseline</u> <u>12 wk</u> <u>p-value</u> Trandolapril 92 ± 10 89 ± 10 NS Losartan 93 ± 9 92 ± 10 NS Mean glucose infusion rate (GIR) (mg/min/kg): <u>Baseline</u> <u>12 wk</u> <u>p-value</u> Trandolapril 6.67 ± 0.56 7.99 ± 0.65 < 0.05 Losartan 6.74 ± 0.47 6.96 ± 0.50 NS p = significant (but not specified) for between-group comparison **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Formosa, Bellomo,	Geographical location: Rome, Italy	Number of patients: N = 60 - Screened for inclusion: NR	**1) Blood pressure:** Repeat ABPM after 12 weeks therapy	**General comments:**

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Iori, et al., 2009 **#1655**	Study dates: NR Funding source: None Interventions: 1. Telmisartan: 40 mg/d. Increased to 80 mg/d at week 4, if indicated. 2. Valsartan: 80 mg/d. Increased to 160 mg/d at week 4, if indicated. 3. Ramipril: 2.5 mg/d. Increased to 5 mg/d at week 2, if indicated, and then to 10 mg/d at week 4, if indicated. Were additional anti-hypertension medications allowed: NR If Yes to above, was this done: NR Study design: Other: Prospective and open-label Blinding: - Patients: No - Providers: No - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: NR Washout period(s): NA Duration of treatment: 12 weeks	- Eligible for inclusion: NR - Randomized: NR (20 patients allocated to each intervention group, but unclear if randomly assigned) - Began treatment: 20 - Completed treatment: NR - Withdrawals/losses to followup: NR Age: Mean (SD): NR Median: NR Range: All > 65 years **Sex (n [%]):** Female: NR Male: NR Race/ethnicity (n [%]): NR **Baseline blood pressure:** Average of 2-3 readings while sitting, after resting for 5 minutes, for baseline measure. Outcomes measured by 24-hr AMBP. **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: - HTN grades 1, 2, or 3 according to ESH/ESC 2007 Guidelines - Metabolic syndrome (diagnosed according to the guidelines of the	(compared with baseline ABPM): <u>Average BP reduction in the 24 hrs between one administration of the drug and the next:</u> Telmisartan: 13.8 (SBP); 9.5 (DBP) Valsartan: 11.5 (SBP); 8.0 (DBP) Ramipril: 11.8 (SBP); 7.5 (DBP) <u>Average BP reduction in the first 18 hrs of the interval:</u> Telmisartan: 14.55 (SBP); 9.9 (DBP) Valsartan: 13.2 (SBP); 8.8 (DBP) Ramipril: 13.0 (SBP); 8.3 (DBP) <u>Average BP reduction in the last 6 hrs of the interval:</u> Telmisartan: 11.7 (SBP); 8.3 (DBP) Valsartan: 9.0 (SBP); 5.7 (DBP) Ramipril: 8.3 (SBP); 5.3 (DBP) <u>Average BP reduction in the last 4 hrs of the interval:</u> Telmisartan: 12.5 (SBP); 8.5 (DBP) Valsartan: 8.9 (SBP); 5.6 (DBP) Ramipril: 8.5 (SBP); 5.4 (DBP) **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR	None Quality assessment: Overall rating: Poor Comments: - Appears to be non-random allocation to intervention groups - Inadequate reporting of patient characteristics, methods, and results - Inappropriate statistical analysis **Applicability:** - Conducted in Italy Inadequate reporting of patient recruitment and selection, adherence, and co-interventions

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		National Cholesterol Education Program Adult Treatment Panel III, proposed by the AHA in 2005)	**8) Lipid levels:** NR	
	Duration of post-treatment followup: NA		**9) Progression to type 2 diabetes:** NR	
		Exclusion criteria: - History of coronary illness, cardiac failure, or stroke - Hepatic or renal insufficiency or with secondary HTN - Use of pharmaceutical products which might influence BP such as β-agonists and antagonists, nitroglycerine, theophylline, inhibitors of monoamine oxidase, phenothiazine, tricyclic antidepressants and other antihypertensive drugs	**10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Franke, 1997 **#1581**	Geographical location: Saarlouis, Germany Study dates: NR Funding source: NR Interventions: - Placebo (n = 65) - Candesartan 4 mg (n = 66) - Candesartan 8 mg (n = 68) - Candeartan 12 mg (n = 65) - Enalapril 10 mg (n = 71) No dose titration; no co-interventions Study design: RCT, parallel-group Blinding: - Patients: Yes	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 364 - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR (11 due to AEs, rest uncertain) - ITT population = 335 Age: Mean (SD): NR Median: NR Range: NR **Sex (n [%]):** NR Race/ethnicity (n [%]): NR **Baseline blood pressure:** NR Seated trough BP measured	**1) Blood pressure:** Baseline BP values NR (except DBP in Figure 1) Mean post-treatment BP values NR Mean changes (± SD) in seated trough DBP (mm Hg) at 12 wk: Candesartan 4 mg (n = 66): -8.4 ± 10.5 Candesartan 8 mg (n = 68): -10.5 ± 9.9 Candesartan 12 mg (n =65): -10.0 ± 10.0 Enalapril 10 mg (n = 71): -10.6 ± 9.8 No between-group statistical results shown Response rates (reduction in seated DBP of ≥ 10 mm Hg and/or seated DBP < 90 mm Hg): Candesartan 4 mg (n = 66): 53.0% Candesartan 8 mg (n = 68): 69.1% Candesartan 12 mg (n =65): NR Enalapril 10 mg (n = 71): 69.0% No between-group statistical results shown	**General comments:** - Short report with minimal details Quality assessment: Overall rating: Poor Comments: - Extremely brief, few details **Applicability:** - Minimal information provided about study population, recruitment sites, etc.

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: NR Baseline/run-in period: Washout of at least 2 weeks, followed by 2-week placebo run-in Duration of treatment: 12 weeks Duration of post-treatment followup: NA	using a fully automated device (Bosotron 2) Baseline values NR **Concurrent medications (n [%]):** NR; concomitant treatment with other antihypertensives not permitted **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: - Age 18-70 yr - Mild-to-moderate essential hypertension (sitting DBP 95-114 mmHg) Exclusion criteria: None specified	**2) Rate of use of a single antihypertensive agent for BP control:** No other antihypertensives permitted **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** 186 adverse events, equally distributed among all groups Patients experiencing ≥ 1 AE: Candesartan groups: 28-33% Enalapril: 35% Withdrawals due to AEs: 11 (treatment groups not specified) **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Ghiadoni, Magagna, Versari, et al., 2003	Geographical location: NR Study dates: June 1999-Dec 2001	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 180	**1) Blood pressure:** At 6 months: Telmisartan Perindopril SBP	**General comments:** - Patients in multiple arms with small control group

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
#1584	Funding source: NR Interventions: Multi-therapy trial (nifedipine, amlodipine, atenolol, nebivolol, telmisartan, and perindopril); total study was 40 normotensive controls and 180 treated patients - Telmisartan 80 to 160 mg (n = 29) - Perindopril 2 to 4 mg (n = 28) HCTZ 12.5 mg added if needed to each compound Study design: RCT, parallel-group Blinding: - Patients: NR - Providers: NR - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: None Duration of treatment: 6 months Duration of post-treatment followup: NR	- Began treatment: 180 - Completed treatment: 168 - Withdrawals/losses to followup: 12, all due to treatment failure (required additional drugs beyond those specified in study protocol) Age: Mean (SD): 50.5 ± 10 Median: NR Range: NR **Sex (n [%]):** Female: 22/57 = 37% Male: 36/57 = 63% Race/ethnicity (n [%]): NR **Baseline blood pressure:** Mean of 3 measurements taken at 3-min intervals using an automatic digital device (Omron HEM-705CP) Telmisartan / Perindopril SBP 151 ± 10 / 153 ± 9 DBP 100 ± 7 / 100 ± 6 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** Outpatient clinics	133 ± 10 / 134 ± 10 DBP 86 ± 5 / 86 ± 6 Responders at 6 mo (BP < 140/90 mm Hg): Telmisartan: 22/29 (76%) Perindopril: 22/28 (79%) **2) Rate of use of a single antihypertensive agent for BP control:** HCTZ added in 21% of telmisartan patients (6/29) and 25% of perindopril patients (7/28) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** 164 out of 180 – 16 BP rose too high to continue in study protocol **8) Lipid levels:** Total cholesterol: Telmisartan / Perindopril Baseline 218 ± 24 / 214 ± 252 6 mo 216 ± 21 / 209 ± 21 HDL: Telmisartan / Perindopril Baseline 53 ± 15 / 53 ± 11 6 mo 52 ± 14 / 53 ± 9	Quality assessment: Overall rating: Poor Comments: - No comment on blinding of endpoints - Study population not well defined (how they were recruited, which patients from which groups dropped out, etc.) - No data on race/ethnicity of subjects - No data on safety/adverse events **Applicability:** - Limited by few comorbidities and multiple comparisons

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Inclusion criteria: - Patients with essential hypertension who were never treated or had discontinued treatment for HTN - Non-smokers or < 5 cigarettes per day - Alcohol consumption < 50 mg/day Exclusion criteria: - Diabetes - Renal dysfunction - Total cholesterol > 240	LDL: <u>Telmisartan</u> <u>Perindopril</u> Baseline 136 ± 16 131 ± 18 6 mo 134 ± 17 128 ± 15 **9) Progression to type 2 diabetes:** Plasma glucose levels remained essentially unchanged (see immediately below) **10) Markers of carbohydrate metabolism/diabetes control:** Plasma glucose: <u>Telmisartan</u> <u>Perindopril</u> Baseline 97 ± 8 96 ± 7 6 mo 97 ± 8 97 ± 5 **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Gregoire, Moisan, Guibert, et al., 2001 **#1585**	Geographical location: 173 pharmacies across Canada Study dates: Feb 1996-Oct 1997 Funding source: Merck Frosst Canada Interventions: - Losartan (n = 80) - ACEI (n = 369) - CCB (n = 214) Study design: Prospective cohort	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: 692 recruited - Completed treatment: 663 - Withdrawals/losses to followup: 29 (9 lost to followup, 20 discontinued before end of study for reasons other than AEs) Age: Mean (SD): 58.3 Median: NR	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** ≥ 1 AE related to antihypertensive medication: Losartan: 42/80 (52.5%)	**General comments:** - Obvious limitations from prospective cohort design with no info on those screened but not included - Statistically significant differences at baseline between 3 groups with respect to proportion who were "new users" vs. "discontinuers" and numbers who switched previous medication due to AEs and uncontrolled hypertension - No data on BP

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	study Blinding: - Patients: No - Providers: No - Assessors of outcomes: Yes (research assistants unaware of study's objectives telephoned participants) Was allocation concealment adequate?: NR Baseline/run-in period: NA Duration of treatment: NR Duration of post-treatment followup: 3 months (assessments at baseline, 1mo, and 3mo)	Range: 20.4-87.7 **Sex (n [%]):** Female: 369 (55.7%) Male: 294 (44.3%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** 173 pharmacies in Canada Inclusion criteria: - HTN patients ≥ 18 yr - Received 1st prescription for losartan, ACEI, or CCB as hypertensive monotherapy Exclusion criteria: - Pregnant women - Taking other anti-HTN meds - Taking meds for CHF or angina - Previously given samples of study medication by their physicians	ACEI: 222/369 (60.2%) CCB: 149/214 (69.6%) Odds of reporting an AE were significantly higher among patients treated with an ACEI (adjusted odds ratio = 1.78; 95% CI, 1.02 to 3.12) or a CCB (2.65; 1.47 to 4.78) than among patients treated with losartan. Estimates adjusted for age, sex, level of education, number of symptoms due to health problems pereived the week prior to entering the study, prior use of antihypertensive drugs, current use of any other medication, insurance coverage, and duration of hypertension). **6) Specific adverse events:** Specific AEs (numbers are n [%]): <u>Losartan</u> <u>ACEI</u> <u>CCB</u> Dizziness 16 (20) 49 (13.3) 51 (23.8) Headache 11 (13.8) 53 (14.4) 49 (22.9)* Dry cough 4 (5.0) 55 (14.9)* 5 (2.3) Tiredness 4 (5.0) 23 (6.2) 15 (7.0) Nausea 2 (2.5) 19 (5.1) 17 (7.9)* Dry mouth 4 (5.0) 19 (5.1) 11 (5.1) Swollen ankles 2 (2.5) 1 (0.3) 27 (12.6)* * Adjusted odds of experiencing AE significantly greater than with losartan (see Table 3 for details) **7) Persistence/adherence:** NR	Quality assessment: Overall rating: Poor Comments: - Numbers screened and eligible NR - AEs relatively well reported - Adjustment generally good, but lacks adjustment for comorbid conditions (e.g., CHF) which could confound presence of AEs **Applicability:** - No assessment of severity of disease or comorbidities - No adjustment or evaluation for comorbitiies or severity of disease - Patients selected by pharmacies - No blood pressure data

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			8) Lipid levels: NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Guntekin, Gunes, Tuncer, et al., 2008 **#77**	Geographical location: Van, Turkey Study dates: NR Funding source: NR Interventions: - Quinapril 20 mg/day (n = 18). If optimal BP not achieved after 14 days, dose increased up to 40 mg twice daily. - Irbesartan 150 mg/day (n = 20). If optimal BP not achieved after 14 days, dose increased up to 300 mg/day. Were additional anti-hypertension medications allowed: No, but patients requiring additional meds were excluded post-randomization Study design: RCT, parallel-group Blinding:	Number of patients: N = 38 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 65 - Began treatment: 65 - Completed treatment: 38 - Withdrawals/losses to followup: 27 total: 12 lost to followup; 6 non-compliant; 9 required additional therapy Age: Mean (SD): 56.5 ± 11 **Sex (n [%]):** Female: 26 (68.4%) Male: 12 (31.6%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Seated, resting with mercury manometer. Highest of two arms used. Quinapril: 198.9/117.5 (SD 19.1/13.8)	**1) Blood pressure:** P values for between-group differences not reported ("no significant differences between groups"). 6- and 12-month BP compared to baseline P < 0.001 for all readings 6 months (SD): Quinapril: 157.6/90.5 (10.6/5.9) Irbesartan: 156.7/91.7 (12.3/6.1) 12 months (SD): Quinapril: 145.5/90.3 (12.9/8.6) Irbesartan: 149.5/91.5 (14.7/7.9) **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR	**General comments:** Primary focus on ECG changes Quality assessment: Overall rating: Poor Comments: - Limited description of protocol - Analysis was per-protocol and not ITT **Applicability:** - Looks like 65 actually randomized, but only report data on 38 completing the trial; therefore, was per protocol analysis (not ITT) - Limited reporting on protocol, including BP measurement, degree of dose titration in each arm, patient recruitment - Small study done only in Turkey

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Patients: NR (probably not) - Providers: NR (probably not) - Assessors of outcomes: Yes, but only for ECG- and echo-measured outcomes Was allocation concealment adequate?: NR Baseline/run-in period: NA Duration of treatment: 12 months Duration of post-treatment followup: No data reported after 12-month treatment period	Irbesartan: 198.0/116.7 (SD 16.7/9.5) **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** Smoking: Quinapril: 3 (16.6) Irbesartan: 4 (20.0) Hyperlipidemia: Quinapril: 6 (33.1) Irbesartan: 5 (25.0) **Recruitment setting:** NR Inclusion criteria: New diagnosed hypertension Exclusion criteria: - Systolic BP > 240 mmHg and diastolic BP > 130 mmHg - Secondary HTN - AF, left bundle branch block, ventricular tachycardia or frequent ventricular premature beats - Moderate to severe valvular disease - Atrial enlargement - LVEF ≤ 50% - Hepatic or renal failure - Chronic obstructive lung disease - DM - Known or suspected CAD as assessed by medical history and symptoms - Estimated pulmonary artery	**7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** No significant between-group difference (p values and data not reported). Both reduced posterior wall thickness (data not reported) Quinapril: p = 0.004 Irbesartan: p = 0.016 **12) Creatinine/GFR:** NR **13) Proteinuria:** NR **14) Atrial fibrillation:** NR, but data on P-wave duration and P-wave dispersion reported as well	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		systolic pressure (PASP) > 30 mmHg - Beta-blocker or anti-arrhythmic drug use for any reason (e.g. migraine, analgesia, seizure, etc.) - Patients requiring further antihypertensive medication beyond study dosages to achieve BP of < 140/90 mmHg were also excluded.		

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Hasford, Mimran, and Simons, 2002 **#1587**	Geographical location: France, Germany, and UK Study dates: Initial antihypertensive prescription given Oct 1997-Sep 1998; patients followed retrospectively for 1 yr Funding source: Sanofi-Synthelabo and Bristol-Myers Squibb Interventions: Monotherapy with one of the following single agents: - ACEIs: 333 - Irbesartan: 380 - Losartan: 188 - Valsartan: 69 - Candesartan: 82 - Eprosartan: 35 - Beta-blockers (BBs): 441 - Calcium channel blockers (CCBs): 466 - Diuretics: 422 Dose titration and co-interventions: Dose titration of initial medication allowed Study design: Retrospective cohort database study Matched those initially not prescribed irbesartan to those prescribed irbesartan by diabetes, angina, CVA, CHF, MI	Number of patients: - Screened for inclusion: 3026 - Eligible for inclusion: 2416 - Randomized: NA - Began treatment: NA - Completed treatment: NA - Withdrawals/losses to followup: NR Age: Mean (SD): 60.3 Median: NR Range: NR **Sex (n [%]):** Female: 1269 (54%) Male: 1147 (46%) Race/ethnicity (n [%]): NR, presumably 100% Caucasian **Baseline blood pressure:** Method of assessing BP not described SBP / DBP ACEIs: 159.8 ± 22.5 / 94.6 ± 14.1 Irbesartan: 164.3 ± 22.4 / 93.5 ±16.7 Losartan: 160.4 ± 19.5 / 91.4 ± 13.8 Other ARBs: 164.7 ± 21.8 / 95.9 ± 20.6 BBs: 162.2 ± 23.6 / 94.4 ± 14.4 CCBs: 162.9 ± 22.1 / 93.6 ± 17.5	**1) Blood pressure:** BP reduction not a predefined study outcome Minimal results reported for subgroup of all patients with on-treatment BP data (n = 717); precise timepoint(s) of BP measurement(s) not specified; not clear whether restricted to patients who persisted with their original monotherapy General estimating equation (GEE) analysis showed that, in above-described subgroup, patients who were originally prescribed irbesartan had a greater average decrease in SBP (5.91 mm Hg; p = 0.053) and DBP (4.10 mm Hg; p = 0.090) than patients who were initially prescribed losartan and a greater average decrease in SBP (4.95 mm Hg; p = 0.022) and DBP (3.59 mm Hg; p = 0.053) than patients who were initially prescribed any of the remaining agents **2) Rate of use of a single antihypertensive agent for BP control:** Assessed on basis of prescriptions filled By 1 yr: 46.8% persisted with initially prescribed monotherapy (see below, under Persistence/adherence) 12.9% (9% irbesartan, 8% losartan, 13.6% all other agents) had switched to a different single agent 23.8% had been prescribed adjunctive antihypertension treatment in addition to initially prescribed med (16.1% irbesartan,	**General comments:** None Quality assessment: Overall rating: Fair Comments: - Does not report those who were lost from the system at 1 yr - Outcome measured not useful (lumped together multiple reasons for not being on monotherapy after 1 yr) **Applicability:** - Does not report prevalence of the comorbidities patients were matched on (diabetes, angina, CVA, CHF, MI)

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Diuretics 160.7 ± 20.4 93.8 ± 12.6	24.5% losartan, 25.3% all other agents)	
	Blinding: - Patients: NA - Providers: NA - Assessors of outcomes: NA	**Concurrent medications (n [%]):** NR	**3) Mortality:** NR **4) Morbidity:** NR	
	Was allocation concealment adequate?: NA	**Comorbidities (n [%]):** NR	**5) Safety:** 12.9% overall (9% irbesartan, 8% losartan, 13.6% all other agents) switched to another agent and 16.5% (14.2% irbesartan, 22.9% losartan, 16.6% all other agents) discontinued all antihypertensive therapy , but not clear whether this had to do with efficacy or AEs or something else	
	Baseline/run-in period: NA Duration of treatment: 1-yr follow up after identification Duration of post-treatment followup: NA	**Recruitment setting:** Database study from a health database maintained in UK, France, and Germany that covers "hundreds" of practices that "represent the characteristics of the general medicine practices in each country"	**6) Specific adverse events:** NR	
		Inclusion criteria: - Newly diagnosed hypertension (< 1 yr) - Initial therapy with single agent	**7) Persistence/adherence:** Persistence status determined on basis of filled prescriptions See outcome 2, above, for overall persistence rates	
		Exclusion criteria: - Hypertension > 1 yr - Initial prescription for dual agents	Persistence by treatment group (defined as percentage of patients who remained on their initially prescribed monotherapy at 1 yr):	

	Persistence
ACEIs	42%
Irbesartan	60.8%*
Losartan	44.7%
Other ARBs	51.3%
BBs	49.7%
CCBs	43.6%
Diuretics	34.4%

* p ≤ 0.001 for irbesartan vs. diuretics, ACEIs, CCBs, BBs, and losartan; p ≤ 0.009

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td></td><td></td><td>for irbesartan vs. other ARBs

8) Lipid levels: NR

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: NR

11) LV mass/function: NR

12) Creatinine/GFR: NR

13) Proteinuria: NR</td><td></td></tr>
<tr><td>Hasford, Schroder-Bernhardi, Rotten-kolber, et al., 2007

#166</td><td>Geographical location: 309 practices of General Practitioners and Internists throughout Germany

Study dates: Sep 2000 – May 2001

Funding source: “Completely independent of pharmaceutical sponsors”

Interventions:
Compared medications as a class:
Diuretics
Beta blockers
Calcium antagonists
ACEIs
AIIRA (ARBs)

Were additional anti-hypertension medications allowed: Yes</td><td>Number of patients: N = 13,763
- Screened for inclusion: NR
- Eligible for inclusion: 13,763
- Randomized: NA
- Began treatment: 13,763
- Completed treatment: See results
- Withdrawals/losses to followup: NA (inclusion required at least 3yrs f/u data)

Age:
Mean (SD): 65

Sex (n [%]):
Female: 7707 (56%)
Male: 6056 (44%)

Race/ethnicity (n [%]): NR

Baseline blood pressure: NR

Concurrent non-hypertension medications (n [%]): NR</td><td>1) Blood pressure: NR

2) Rate of use of a single antihypertensive agent for BP control: NR

3) Mortality: NR

4) Morbidity: NR

5) Safety: NR

6) Specific adverse events: NR

7) Persistence/adherence:
Persistence with initial drug class – median days, year 1, 2, 3
<table><tr><td></td><td>Med days</td><td>% at year 1</td><td>% at year 2</td><td>% at year 3</td></tr><tr><td>ACEI</td><td>98</td><td>28.2</td><td>18.6</td><td>14.0</td></tr><tr><td>ARB</td><td>100</td><td>26.4</td><td>15.3</td><td>10.6</td></tr><tr><td>ARB Comb</td><td>173</td><td>35.6</td><td>24.4</td><td>17.7</td></tr><tr><td>Other+</td><td>0</td><td>12.9</td><td>5.6</td><td>3.2</td></tr></table></td><td>General comments:
Not clear that all prescriptions were for hypertension (patient just had to have a recent diagnosis of hypertension). Several of these medications have other indications.

Quality assessment:
Overall rating: Poor

Comments:
Provides some useful information in estimating the possible range of medication persistence. Would be good to see results in the context of other observational studies on persistence, as seems unlikely that numbers reported here reflect discontinuation due to intolerability or side effects.

Applicability:
- Retrospective cohort with low-quality data provides limited</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td>If Yes to above, was this done: Observational study, so determined by clinician

Study design: Retrospective cohort

Blinding: No

Was allocation concealment adequate?: NA

Baseline/run-in period: NA

Duration of treatment: Patients followed for up to 3years after 1st antihypertension prescription

Duration of post-treatment followup: NA</td><td>Comorbidities (n [%]):
Diabetes: 4020 (29.2%)
CHD: 4628 (33.6)
Lipid disorders: 7135 (51.8)
Obesity: 1616 (11.7)
Diabetes and lipid disorders: 2564 (18.6)

Recruitment setting: Record abstraction from IMS Disease Analyzer; all patients seen in German health care system

Inclusion criteria:
- Newly diagnosed with HTN and had been prescribed an initial treatment with either monotherapy or a specified free or fixed combination of two antihypertensive drugs
- Required to have followup data for 3 years

Exclusion criteria: NR</td><td>ACEI

Persistence with any drug class – median days, year 1, 2, 3

<table><tr><th></th><th>Med days</th><th>% at year 1</th><th>% at year 2</th><th>% at year 3</th></tr><tr><td>ACEI</td><td>137</td><td>32.5</td><td>22.1</td><td>17.1</td></tr><tr><td>ARB</td><td>168</td><td>32.2</td><td>19.2</td><td>14.0</td></tr><tr><td>ARB Comb</td><td>208.5</td><td>39.5</td><td>26.8</td><td>19.6</td></tr><tr><td>Other+ ACEI</td><td>392.5</td><td>52.3</td><td>37.5</td><td>31.2</td></tr></table>
Also presents data as frequency of < 4 prescriptions within 3 years or the persistence rates after 3 years

8) Lipid levels: NR

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: NR

11) LV mass/function: NR

12) Creatinine/GFR: NR

13) Proteinuria: NR</td><td>information about reasons for discontinuation (doctor-based decision vs. patient-based)
- Unclear that all meds were used for hypertension. The numbers for diuretics in particular suggest these may have been used for short-term needs (e.g., volume overload)
- Number discontinuing surprisingly low</td></tr>
<tr><td>Hermida, Ayala, Khder, et al., 2008

#24</td><td>Geographical location: Santiago de Compostela, Spain

Study dates: Jan 2005 – Mar 2006

Funding source: Grants from Novartis Pharma AG, Basel Switzerland; Dirección General</td><td>Number of patients: N = 148
- Screened for inclusion: 244
- Eligible for inclusion: 157
- Randomized: 157
- Began treatment: 157
- Completed treatment: 148
- Withdrawals/losses to followup: 6 lost to followup (3 each arm); 3 discontinued treatment (2</td><td>1) Blood pressure:
Seated 48-hour trough (last dose of medication was 48 hours before this):
Valsartan: 139.5/85.0 (17.1/8.2)
Enalapril: 145.9/87.5 (15.4/7.5)
P value for SBP = 0.026; for DBP = 0.20

Averaged 24-hour mean ABPM reduction (represents mean 24-hour reduction in BP</td><td>General comments:
None

Quality assessment:
Overall rating: Good

Comments:
Very well done study, but most of the data reflect BP 48 hours after</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	de Investigación, Ministerio de Educación y Ciencia, Madrid, Spain (SAF2006-6254); Xunta de Galicia, Santiago de Compostela, Spain (PGIDIT03-PXIB-32201PR); Hospital Clinico Universitario, Santiago de Compostela; and Vicerrectorado de Investigación, University of Vigo, Vigo, Spain. The funding bodies had no role in the analysis and interpretation of the data, the writing of the report, or the decision to submit the manuscript for publication. Interventions: - Valsartan 160 mg daily (n = 79) - Enalapril 20 mg daily (n = 78) Were additional anti-hypertension medications allowed: No Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: Yes Was allocation concealment adequate?: Yes Baseline/run-in period: NA Duration of treatment: 16 weeks Duration of post-treatment	valsartan, 1 enalapril) Age: Mean (SD): 45.8 (10.7) **Sex (n [%]):** Female: 64 (43.2%) Male: 84 (56.8%) Race/ethnicity (n [%]): Spanish 148 (100%) **Baseline blood pressure:** Mean of 6 resting seated clinic BP measurements: Valsartan: 156.0/95.2 (13.2/7.4) Enalapril: 154.2/92.5 (10.8/6.3) **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** Hypertension and vascular risk unit of the Hospital Clinico Universitario, Santiago de Compostela, Spain Inclusion criteria: Age ≥ 18 years and a diagnosis of grade 1 or 2 essential HTN as determined by conventional BP measurement (SBP 140-179 mmHg or DBP 90-109 mmHg) and corroborated by 48-hour ambulatory BP monitoring at the time of recruitment (awake mean BP of > 135/85 mmHg or an asleep mean BP of >120/70	measured over 48 hrs since last med dose) Valsartan: 13.3/10.5 Enalapril: 8.7/6.1 Unclear if between-group difference is statistically significant for SBP (not labeled in Figure 2, but text suggests it is); between-group difference for DBP P < 0.001 1st 24-hour mean ABPM reduction Valsartan: 12.2/9.7 Enalapril: 11.2/7.8 (no significant difference between groups) Separate data for Awake and Asleep ABPM also reported and were significantly different between the two groups (similar to 24-hour mean). Proportion at goal at end of study for awake, sleep, and mean 24-hour BP Valsartan: 54.1% Enalapril: 39.2% P value for between-group difference = 0.036 **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** None **4) Morbidity:** NR **5) Safety:** See below **6) Specific adverse events:** Valsartan: 2 discontinued treatment (1 dizziness and 1 nausea) Enalapril: 1 discontinued treatment	last dose and are therefore not directly comparable to the majority of our studies. This basically shows that valsartan lasts longer than enalapril, but isn't necessarily more effective (when both taken regularly). **Applicability:** - Data reflect BP 48 hours after last dose and therefore should not be combined with our other BP data. Most useful data point is the 1st 24-hour mean ABPM reduction (as this is directly comparable to other studies).

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	followup: NA	mmHg) Exclusion criteria: - Pregnant women - Shift workers - Heavy drinkers (alcohol intake > 80 g/d), heavy smokers (> 20 cigarettes/d), and heavy exercisers were excluded - Severe arterial HTN (grade 3: > 180/110 mmHg) - Type 1 DM - Secondary arterial HTN and concomitant CV disorders (including unstable angina pectoris, heart failure, stroke, life-threatening arrhythmia, nephropathy, and retinopathy), or MI or coronary revascularization within the past year	(hypertensive crisis) **7) Persistence/adherence:** Valsartan: 5 total discontinued Enalapril: 4 total discontinued **8) Lipid levels:** Total cholesterol at baseline – mg/dL: Valsartan: 215.5 (SD 33.5) Enalapril: 217.2 (SD 36.3) Total cholesterol at 16 weeks (P between groups = 0.42): Valsartan: 210.3 (35.2) Enalapril: 214.9 (32.2) Triglycerides baseline – mg/dL: Valsartan: 112.8 (57.7) Enalapril: 114.9 (67.6) Triglycerides at 16 weeks (P between groups = 0.90): Valsartan: 107.8 (58.6)* Enalapril: 109.1 (65.3) *p = 0.041 versus baseline **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** Baseline fasting glucose (mg/dL): Valsartan: 97.1 (13.5) Enalapril: 95.7 (12.4) P = 0.53 Fasting glucose at 16 weeks: Valsartan: 97.5 (12.1) Enalapril: 98.5 (12.4) P = 0.60	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			11) LV mass/function: NR **12) Creatinine/GFR:** Baseline creatinine (mg/dL) : Valsartan: 0.95 (0.13) Enalapril: 0.92 (0.15) P = 0.55 Creatinine at 16 weeks (mg/dL): Valsartan: 0.95 (0.14) Enalapril: 0.93 (0.14) P = 0.45 **13) Proteinuria:** NR	
Hosohata, Saito, Asayama, et al., 2007 **#225**	Geographical location: ~1500 general practitioner's offices throughout Japan Study dates: May 2001 through Feb 2004 Funding source: Grants from the Japan Cardiovascular Research Foundation and the Japan Arteriosclerosis Prevention Fund Interventions: 3x2 factorial design comparing two different target BP ranges and 3 initial antihypertensive drugs. Step program based on control. Initial dose at discretion of treating physician 1) First step is initial drug monotherapy(CCB, ACEI, ARB) 2) Second step is dose increase	Number of patients: N = 1687 - Screened for inclusion: 2729 - Eligible for inclusion: NR - Randomized: 1687 - Began treatment: 1687 - Completed treatment: 971 with 1-year followup - Withdrawals/losses to followup: 54 (20 CCB, 11 ACEI, 23 ARB) Age: Mean (SD): 59.7 ±10 **Sex (n [%]):** Female: 848 (50.3%) Male: 839 (49.7%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Home BP: CCB: 151/90 (14/10) ACEI: 153/90 (13/10) ARB: 151/89 (13/11)	**1) Blood pressure:** Home BP measurement 6 months: ACEI group: 135/80 (13/10) ARB group: 134/79 (13/9) 12 months: ACEI group: 134/79 (12/9) ARB group: 132/79 (13/8) Casual BP: 6 months CCB group: 133 (SD 16) ACEI group: 136 (SD 16) ARB group: 133 (SD 17) P = 0.03 for comparison among 3 groups 12 months: Numbers not reported, but not statistically significant Rate of BP control (apparently at 12 months, but this is not completely clear): Less intensive group: CCB: 44%	**General comments:** None Quality assessment: Overall rating: Fair Comments: None **Applicability:** - The BP data reflect lowering from multiple medications as a part of protocol, would be wary of directly comparing BP-lowering effects between two agents. - There was high rate of switch from ACE→ARB. Unclear if this was all due to cough or other AE, and unclear how this was categorized in determining which step patients were listed in.

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	of first drug 3) Third step: If patient not controlled on initial drug, then add diuretic 4) Fourth step: Patients randomized to add either an alpha blocker or beta blocker 5) Fifth step: Add any other antihypertensive Were additional anti-hypertension medications allowed: Yes (as described above) If Yes to above, was this done: Per protocol Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: Yes Was allocation concealment adequate?: Yes Baseline/run-in period: NR Duration of treatment: 12 months Duration of post-treatment followup: NA	Office "casual" BP measured twice by physician: CCB: 157/92 (17/12) ACEI: 156/91 (18/12) ARB: 156/91 (17/11) **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** 1500 general practitioners in Japan Inclusion criteria: - Age 40-79 years - Essential HTN - Not on antihypertensive medication - Home BP values ≥ 135 SBP or ≥ 85 mmHg DBP Exclusion criteria: - Contraindications to any of the medications used - Pure systolic HTN (SBP ≥ 135, but DBP < 65) - Pure diastolic HTN (SBP < 110 and DBP ≥ 85) - Severe HTN defined as home BP ≥ 180/120 or office BP ≥ 220/125	ACEI: 43% ARB: 48% (no significant difference) More intensive group: CCB: 21% ACEI: 19% ARB: 19% **2) Rate of use of a single antihypertensive agent for BP control:** Those remaining in Step 1 or 2: CCB: 103 (30%) ACEI: 58 (17%) ARB: 89 (29%) Note: It is unclear in the ACEI arm how authors categorized patients who were intolerant of ACEI, switched to ARB, then were controlled on ARB monotherapy **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Persistence at 12 months: ACEI: 180/328 (55%) ARB: 266/303 (88%) Difficult to assess switch rates from ACEI to ARB. It appears that at least 102 patients in the ACEI arm switched to an ARB at some point. **8) Lipid levels:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			9) Progression to type 2 diabetes: NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Karlberg, Lins, and Hermans-son, 1999 **#1588**	Geographical location: 22 sites, 2 Denmark, 6 Finland, and 14 Sweden Study dates: NR Funding source: NR Interventions: - Telmisartan (20, 40-80 mg) (n = 139) - Enalapril (5, 10-20 mg) (n = 139) Titrated to higher dose if mean DBP > 90 at 4-wk intervals until wk 16, then add HCTZ 12.5-25 mg for DBP > 90 Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: NR Was allocation concealment	Number of patients: - Screened for inclusion: 356 - Eligible for inclusion: NR - Randomized: 278 - Began treatment: 278 - Completed treatment: 251 - Withdrawals/losses to followup: 36, 2 due to lack of efficacy, 27 due to AEs, 7 for administrative or other reasons (note: reported numbers do not total correctly) - ITT population = 272 Age: Mean (SD): 71.0±4.9 Median: NR Range: NR **Sex (n [%]):** Female: 160 (58%) Male: 118 (42%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Trough BP measured 3 times at 2-min intervals after patient	**1) Blood pressure:** Placebo-adjusted mean change from baseline in trough supine BP (mm Hg; means NR): Telmisartan / Enalapril / p-value SBP: -22.1 / -20.1 / 0.350 DBP: -12.8 / -11.4 / 0.074 Response rates (trough supine BP, last available assessment): Definition of "response": Telmisartan / Enalapri DBP < 90: 86 (63%) / 84 (62%) DBP < 90 or decrease ≥ 10 mm Hg vs. baseline: 96 (71%) / 93 (68%) SBP reduced ≥ 10 mm Hg vs. baseline: 95 (70%) / 91 (67%) Note: Also reports subgroup analyses for: - Age < 75 vs. ≥ 75 - Male vs. female	**General comments:** None Quality assessment: Overall rating: Fair Comments: **Applicability:** - No real baseline co-morbidity information - Recruitment strategy not clear, run in period took 20% out - No data on race/ethnicity of subjects

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	adequate?: NR Baseline/run-in period: 3- to 5-wk double-dummy placebo run-in period to determine eligibility Duration of treatment: 26 wk: 16 wk titration; 10 wk maintenance Duration of post-treatment followup: NR	rested in supine position for 5 min using a standard mercury sphygmo-manometer Baseline supine values: Telmisartan / Enalapril SBP 180.6 ± 18.4 / 177.4 ± 16.6 DBP 101.9 ± 5.2 / 100.7 ± 5.1 **Concurrent medications (n [%]):** Outside of HCTZ added per protocol, not assessed or mentioned **Comorbidities (n [%]):** NR (though see Exclusion criteria) **Recruitment setting:** NR – assume outpatient clinics Inclusion criteria: - Age ≥ 65 years with mild to moderate HTN - Mean DBP ≥ 95 and ≤ 114 mmHg at final two consecutive visits of the 3- to 5-wk placebo run-in phase, and if mean supine DBP vary by more than 10 mmHg Exclusion criteria: - Known or suspected secondary hypertension - Hepatic or renal dysfunction - Bilateral renal artery stenosis or post-renal transplant	Results also reported for ABPM **2) Rate of use of a single antihypertensive agent for BP control:** 87 (64%) telmisartan and 84 (63%) enalapril used one agent **3) Mortality:** NR **4) Morbidity:** Quality of life scales administered, but simply states scores were high at baseline in both groups and did not change during study; no quantitative data **5) Safety:** 98/139 patients in each treatment group (71%) experienced ≥ 1 AE. 35 (35%) in the telmisartan group and 52 (37%) in the enalapril group were considered by investigators to have treatment-related AEs. Serious AEs considered by investigators to be treatment-related (number of patients): Telmisartan: - Glaucoma (1) - Strabismus (1) Enalapril: - Dizziness, vertigo and chest pain (1) - Constipation (1) - Stroke (1) - Severe disabling Quincke's angioneurotic edema (1) Withdrawals due to AEs: Telmisartan: 11 (7.9%) Enalapril: (11.5%) **6) Specific adverse events:**	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- NYHA class III or IV CHF - Recent MI or CABG - Clinically relevant arrhythmias - Clinically significant sodium depletion - Hypokalemia or hyperkalemia - Poorly controlled diabetes - Chronic use of oral anti-coagulants - High doses NSAIDs or acetaminophen - Salt substitutes or KCL - Use of investigational drugs - Patients with mean supine SBP > 220 or supine DBP > 114 mm Hg at any time during the placebo run-in phase	Treatment-related AEs (n [%]; n = 139 each group): Telmisartan / Enalapril Any event: 35 (25.2%) / 52 (37.4%) Cough: 9 (6.5) / 22 (15.8) Diarrhea: 6 (4.3) / 3 (2.2) Dizziness: 4 (2.9) / 4 (2.9) HA: 3 (2.2) / 4 (2.9) Flatulence: 2 (1.4) / 2 (1.4) Nausea: 2 (1.4) / 2 (1.4) Increased sweating: 2 (1.4) / 2 (1.4) Erythematous rash: 2 (1.4) / 2 (1.4) Rhinitis: 2 (1.4) / 2 (1.4) Impotence: 2 (1.4) / 1 (0.7) **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			12) Creatinine/GFR: NR **13) Proteinuria:** NR	
Kavgaci, Sahin, Onder Ersoz, et al., 2002 **#1589**	Geographical location: Trabzon, Turkey Study dates: NR Funding source: NR Interventions: - Losartan 50 mg daily (n = 20) - Fosinopril 10 mg daily (n = 10) Dose titration/co-interventions: Amlodipine 5 mg add at 1 mo if BP ≥ 140/85; titrated up to 10 mg if BP still uncontrolled at 2 mo Study design: RCT, parallel-group (open-label) Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: NR Baseline/run-in period: 15-day washout if previously on anti-HTN meds (n = 18) Duration of treatment: 6 mo Duration of post-treatment followup: NA	Number of patients: - Screened for inclusion: - Eligible for inclusion: 33 - Randomized: 33 - Began treatment: 33 - Completed treatment: 33 - Withdrawals/losses to followup: 0 Age: Mean (SD): 52.9 Median: NR Range: 40-66 **Sex (n [%]):** Female: 20 (61%) Male: 13 (39%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Seated trough BP measured using a sphygmomanometer after a 15-min rest; mean of 3 measurements taken at 5-min intervals Losartan Fosinopril SBP 159 ± 21 156 ± 21 DBP 99 ± 11 97 ± 9	**1) Blood pressure:** Mean seated trough BP at 6 mo: Losartan Fosinopril SBP 132 ± 10 136 ± 8 DBP 84 ± 7 84 ± 4 All comparisons with baseline statistically significant Between-group p-values NS **2) Rate of use of a single antihypertensive agent for BP control:** Patients using adjunctive amlodipine: Losartan: 7 (35%) Fosinopril: 4 (31%) **3) Mortality:** No deaths during study **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** Mean total cholesterol (mmol/L): Baseline 6 mo p-value Losartan 5.65 ± 1.24 5.7 ± 1.25NS Fosinopril 5.97 ± 1.3 5.34 ± 0.72< 0.05 Mean triglycerides (mmol/L): Baseline 6 mo p-value	**General comments:** - All patients recommended to be on low-protein diet, ? benefit/ impact Quality assessment: Overall rating: Poor Comments: - Inconsistent use of significant digits raises more general suspicions - Large amounts of missing details **Applicability:** - Patients poorly characterized - Not clear how many other comorbidities present

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Concurrent medications (n [%]): Usual antidiabetic medication continued during trial: Losartan Fosinopril Oral meds 13 (65%) 9 (69%) Insulin 3 (15%) 2 (15%) **Comorbidities (n [%]):** - 100% with diabetes type 2 **Recruitment setting:** Internal medicine outpatient clinics of a university hospital Inclusion criteria: - Type 2 diabetes - SBP 140-180 Exclusion criteria: - Albuminuria > 300 mg/day - Cr Cl < 100 mlLmin - Taking ACEIs or AT1 blockers	Losartan 2.17 ± 1.1 1.66 ± 0.72 < 0.05 Fosinopril 2.36 ± 1.2 1.87 ± 1.0 < 0.05 **9) Progression to type 2 diabetes:** NA **10) Markers of carbohydrate metabolism/diabetes control:** Mean total glucose (mmol/L): Baseline 6 mo p-value Losartan 8.93 ± 3 7.76 ± 1.96 NS Fosinopril 9.87 ± 3.4 9.327 ± 1.9 NS Mean HbA1c (%): Baseline 6 mo p-value Losartan 7.53 ± 2.50 6.58 ± 1.18 NS Fosinopril 8.15 ± 1.64 7.57 ± 1.65 NS **11) LV mass/function:** NR **12) Creatinine/GFR:** Mean creatinine (μmol/L): Baseline 6 mo p-value Losartan 78.7 ± 17.7 84.8 ± 10.6 NS Fosinopril 86.6 ± 17.7 84.8 ± 10.6 NS Mean creatinine clearance (mL/min): Baseline 6 mo p-value Losartan 186.5 ± 68.2 122.2 ± 38.3 < 0.0001 Fosinopril 156.0 ± 56.6 113.1 ± 36.5 < 0.05	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			13) Proteinuria: Mean albumin excretion (mg/day) in subgroup with microalbuminuria: Baseline / 6 mo / p-value Losartan 121 (n = 8) / 54.8 (32.0-264.5) (8.6-261.0) / < 0.05 Fosinopril 154 (n = 7) / 14 (44-300) (10.6-46.0) / < 0.05	
Kloner, Neutel, Roth, et al., 2008 **#79**	Geographical location: 75 centers in the US Study dates: NR Funding source: Pfizer, Inc. Interventions: 1) Quinapril/amlodipine: - Quinapril 20 mg daily x4 weeks - If BP > 130/80 then increase to 40 mg x4 weeks - After 8 weeks, if BP < 130/80, then no change; if > 160/100, then removed from study or given open-label amlodipine - If BP between 130/80 and 160/100, then given amlodipine 5 mg daily x 6 more weeks - After 14 weeks, If BP > 130/80, then amlodipine increased to 10 mg daily 2) Quinapril/placebo: - Quinapril 20 mg daily x4 weeks - If BP > 130/80 then increase to 40 mg x 4 weeks	Number of patients: N = 411 - Screened for inclusion: 1222 - Eligible for inclusion: NR - Randomized: 739 - Began treatment: 739 - Completed treatment: - 739pts included in safety analysis - 711pts included in monotherapy efficacy analysis - 411 patients included in combined therapy efficacy analysis. - Withdrawals/losses to followup: - 112 continued on only monotherapy (54 quinapril, 58 losartan) - 113 discontinued monotherapy treatment (54 quinapril, 59 losartan) Age: Mean (SD): 58.4 ± 9.7 Range: 32-80 **Sex (n [%]):** Female: 179 (43.6%)	**1) Blood pressure:** Seated mercury sphygmomanometer after 10-30 min rest. Used average of 2 readings. A third reading was taken when difference of ≥ 10 mmHg between first 2. **Attainment of BP goal at 20 weeks (< 130/80)** Quinapril/amlodipine: 29/96 (30.2%) Quinapril/placebo: 15/103 (14.6%) Losartan/amlodipine: 29/115 (25.2%) Losartan/placebo: 10/97 (10.3%) No statistically significant difference between quinapril and losartan for BP control (p = 0.25) **Mean change in SBP from baseline to week 14 among those on monotherapy (small subgroup of population)** Quinapril: -8.0 Losartan: -10.6 P = 0.12 **2) Rate of use of a single antihypertensive agent for BP control:** Week 4:	**General comments:** None Quality assessment: Overall rating: Fair Comments: Complicated post-randomization dose adjustments/titration makes primary comparison more convoluted **Applicability:** - The complex protocol with multiple post-randomization titration changes based on BP control makes it difficult to compare ACEI vs. ARB outcomes at time points past 8 weeks. Would therefore be wary about combining data that represents effects among responders vs. non-responders. - Much of the data focuses on comparison of amlodipine vs. placebo add-on and not useful for this review.

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- After 8 weeks, if BP < 130/80, then no change; if > 160/100, then removed from study or given open-label amlodipine - If BP between 130/80 and 160/100, then given placebo daily x 6 more weeks - After 14 weeks, if BP > 130/80, then placebo dose daily 3) Losartan/amlodipine: - Losartan 50 mg daily x4weeks - If BP > 130/80 then increase to 100mg x 4weeks - After 8 weeks, if BP < 130/80, then no change; if > 160/100, then removed from study or given open-label amlodipine - If BP between 130/80 and 160/100, then given amlodipine 5 mg daily x 6 more weeks. - After 14 weeks, if BP > 130/80, then amlodipine increased to 10 mg daily 4) Losartan/placebo: - Losartan 50 mg daily x 4weeks - If BP > 130/80 then increase to 100 mg x 4 weeks - After 8 weeks, if BP < 130/80, then no change; if > 160/100, then removed from study or given open-label amlodipine - If BP between 130/80 and 160/100, then given placebo daily x 6 more weeks - After 14 weeks, If BP > 130/80, then placebo dose daily Were additional anti-	Male: 232 (56.4%) Race/ethnicity (n [%]): White: 286 (69.6%) Black: 70 (17.0%) Asian: 6 (1.5%) Other: 49 (11.9%) **Baseline blood pressure:** Seated mercury sphygmomanometer after 10-30min rest. Used average of 2 readings. A third reading was taken when difference of ≥ 10 mmHg between first 2. Mean mmHg (SD): Quinapril monotherapy (n = 364): 149.3/88.3 (11.1/8.6) Losartan monotherapy (n=375): 149.8/88.0 (11.3/9.1) Quinapril/amlodipine (represents those who made it to next titration; n = 96): 148.2/89.1 (10.1/7.9) Quinapril/placebo (n = 103): 149.7/88.3 (10.2/8.0) Losartan/amlodipine (n = 115): 149.9/88.0 (10.9/9.3) Losartan/placebo (n = 97): 152.1/88.9 (11.1/7.3) **Concurrent non-hypertension medications (n [%]):** 422/431 (97.9%) used at least one other medication Antidiabetic agents (84.0%) Lipid-lowering agents (52.7%) Analgesics (48.3%) Vitamins (29.5%)	Quinapril: n = 351 (13.4%) Losartan: n = 359 (14.2%) P = 0.66 Week 8: Quinapril : n = 333 (18.9%) Losartan : n = 342 (22.2%) P = 0.18 **3) Mortality:** None **4) Morbidity:** NR **5) Safety:** Only 1 serious adverse event related to study treatment (quinapril monotherapy group). Type of event not reported. Discontinuation due to treatment-related adverse event in ACE v. ARB monotherapy: Quinapril: 11/364 (3%) Losartan: 5/375 (1.3%) P = 0.19 **6) Specific adverse events:** Lab abnormalities: Quinapril: 2% Losartan: 3% 1 patient in quinapril + placebo had increased Cr more than 1.3 times upper limit of normal. Specific AEs for combined therapy: Headache: Quinapril/placebo: 5 (4.5%) Losartan/placebo: 5 (4.9%) Upper RTI: Quinapril/placebo: 4 (3.6%) Losartan/placebo: 3 (2.9%)	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	hypertension medications allowed: Yes (as indicated above) If Yes to above, was this done: Per Protocol (see protocol above) Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: 7- to 13-day washout period at front end of trial Duration of treatment: 20 weeks Duration of post-treatment followup: NA	Antiinflammatories (27.1%) **Comorbidities (n [%]):** Diabetes 100% **Recruitment setting:** NR Inclusion criteria: - Diagnosis of type 2 DM - On stable glucose-lowering treatment (glycosylated hemoglobin ≤ 9.0%) for at least 2 months - Patients receiving no antihypertensive treatment had to have an SBP of 140-170 mmHg and/or a DBP of 85-100 mmHg; patients on antihypertensive monotherapy had to have an SBP of 140-155 mmHg and/or a DBP of 85-100 mmHg; patients who were using any antihypertensive fixed-dose combination product were required to have an SBP of 135-150 mmHg and/or a DBP of 80-90 mmHg; patients were not permitted to take any antihypertensive agents other than the study medications for the duration of the trial Exclusion criteria: - History of accelerated/malignant HTN - MI, coronary artery bypass, intracoronary interventions, stroke, or transient ischemic attack within 6 months of screening	Cough: Quinapril/placebo: 3 (2.7%) Losartan/placebo: 0 Peripheral edema: Quinapril/placebo: 1 (0.9%) Losartan/placebo: 2 (2.0%) Dizziness: Quinapril/placebo: 0 Losartan/placebo: 2 (2.0) **7) Persistence/adherence:** Quinapril: 54/364 discontinued treatment Losartan: 59/375 discontinued treatment **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** Cr changes only reported for comparison of amlodipine add-on vs. placebo. **13) Proteinuria:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Unstable angina, impending infarction, heart failure, and chronic sustained or uncontrolled cardiac arrhythmias - Secondary HTN of any etiology - Renal impairment (serum creatinine >2.0 mg/dL) -Severe hepatic impairment - History of intolerance/ hypersensitivity to CCBs, ARBs, or ACEIs		
Koylan, Acarturk, Canberk, et al., 2005 **#1590**	Geographical location: Turkey Study dates: May 2000-May 2001 Funding source: NR Interventions: - Irbesartan (n = 337) - ACE inhibitors (n = 298) - CCB (n = 308) Administered "according to approved prescribing guidelines" (details not provided) Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: No, consecutive patients allocated to treatment group in order (max of 6	Number of patients: - Screened for inclusion: 1053 - Eligible for inclusion: 998 - Randomized: NA - Began treatment: 983 - Completed treatment: 872 - Withdrawals/losses to followup: 118 (25 due to AEs; 8 due to lack of efficacy; 85 failed to return) Age: Mean (SD): 52.7 to 54 Median: NR Range: NR **Sex (n [%]):** Female: 56.6% Male: 43.4% Race/ethnicity (n [%]): NR **Baseline blood pressure:** BP measured in morning after 15 min of rest in the supine position Baseline values (± SEM): Irbe ACE CCB	**1) Blood pressure:** No quantitative data reported. Investigators reported no significant differences among the three treatments for: - Reduction in supine SBP and DBP values (vs. baseline) at 1, 3, and 6 months - Percentage of patients with normalized SBP and DBP (≤ 140 mmHg and ≤ 90 mmHg, respectively) at 1, 3, and 6 months **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Irbesartan ACE CCB Any AE 54 (14.3%) 76 (25.5%) 60 (19.5%) P = 0.001 Withdrawals due to AEs: Irbesartan: 0 ACEI: 23/298 (7.7%)	**General comments:** None Quality assessment: Overall rating: Poor Comments: - Used supine BP - Primary objective was to evaluate compliance, not efficacy **Applicability:** - Unusual recruitment strategy that seems highly susceptible to selection bias, as reflected by baseline differences in Table 1

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	patients/physician) Baseline/run-in period: None Duration of treatment: 6 months Duration of post-treatment followup: NR	Supine 160.9 159.6 160.7 SBP ± 16.2 ± 15.2 ± 14.0 Supine 96.2 96.5 95.9 DBP ± 7.4 ± 7.5 ± 7.2 **Concurrent medications (n [%]):** None **Comorbidities (n [%]):** LVH 6.6-8.9% Angina/previous MI 5.4-6.3% Prior cor revasc 1.4-2.8% Heart failure <1-1.8% Stroke/TIA 0-1.1% Nephropathy <1-3.6% Periph art disease<1- 2.9% Retinopathy 2.4-2.9% **Recruitment setting:** Patients recruited by internists or cardiologists at multiple university hospitals Inclusion criteria: - Age > 18 yr - Mild-to-moderate HTN (90 ≤ DBP ≤ 110 mm Hg) - Newly diagnosed with HTN or patients on HTN monotherapy for whom a change in treatment was indicated Exclusion criteria: - Secondary HTN - DBP ≥ 110 mmHg	CCB: 2/308 (< 1%) **6) Specific adverse events: n (%)** Irbe ACE CCB Ankle edema 3 (<1%) 5 (1.7%) 20 (6.5%) Constipation 6 (1.6) 2 (<1) 10 (3.2) Cough 3 (<1) 28 (9.4) 4 (1.3) Dry mouth 14 (3.7) 19 (6.4) 11 (3.6) Dizziness 4 (1.1) 7 (2.3) 5 (1.6) Headache 7 (1.9) 12 (4.0) 7 (2.3) Nausea 7 (1.9) 9 (3.0) 3 (<1) Feeling sick 15 (4.0) 7 (2.3) 14 (4.5) Pyrosis 9 (2.4) 8 (2.7) 6 (1.9) Insomnia 6 (1.6) 7 (2.3) 8 (2.6) **7) Persistence/adherence:** A higher proportion of patents receiving irbesartan took their daily dose of medication than ACE or CCB (p = 0.0005) (see Figure 1) **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td></td><td>- Currently treated with 2-3 anti-HTN drugs or combo agents
- Pregnant or lactating
- Neurological or mental disorders
- MI or CVA < 6 mo
- Severe renal or liver failure</td><td>12) Creatinine/GFR: NR

13) Proteinuria: NR</td><td></td></tr>
<tr><td>Lachaine, Petrella, Merikle, et al., 2008

#117</td><td>Geographical location: Quebec, Canada

Study dates:
Index dates: Jan 1, 2000 – Dec 31, 2001
Data obtained Jan. 1 – Dec. 31, 2003

Funding source: Pfizer Canada Inc., Kirkland, Canada

Interventions:
ACEI (n = 1731)
ARB (n = 962)
CCB (n = 1219)
BB (n = 1143)
Diuretic (n = 1741)

Were additional anti-hypertension medications allowed: Yes

If Yes to above, was this done: At discretion of clinician

Study design: Other – retrospective cohort study

Blinding:
- Patients: NA
- Providers: NA</td><td>Number of patients: N = 4561
- Screened for inclusion: Random sample of 150,000 from over 3 million
- Eligible for inclusion: 4561
- Randomized: NA
- Began treatment: 4561
- Completed treatment: NA
- Withdrawals/losses to followup: NA

Age:
Mean (SD): 68.6 ±12.4
Range:
< 40: 97 (2.1%)
40 – 59: 859 (18.8%)
60 – 79: 2841 (62.3%)
> 80: 764 (16.8%)

Sex (n [%]):
Female: 2792 (61.2%)
Male: 1769 (38.8%)

Race/ethnicity (n [%]): NR

Baseline blood pressure: NR

Concurrent non-hypertension medications (n [%]):
Two meds 32%
Three meds 19%
Four meds 10%</td><td>1) Blood pressure: NR

2) Rate of use of a single antihypertensive agent for BP control:
39% (not broken down by treatment)

3) Mortality: NR

4) Morbidity: NR

5) Safety: NR

6) Specific adverse events: NR

7) Persistence/adherence:

<table><tr><th>Drug</th><th>Persistence</th><th>Adherence</th></tr><tr><td>ACEI</td><td>58.9%</td><td>64.9%</td></tr><tr><td>ARB</td><td>60.9%</td><td>65%</td></tr><tr><td>CCB</td><td>64.3%</td><td>64.2%</td></tr><tr><td>BB</td><td>69.3%</td><td>60.3%</td></tr><tr><td>Diuretic</td><td>52.8%</td><td>50.9%</td></tr></table>
- Adherence higher in 60-79 year age group
- Adherence lower for patients on 3 or more agents
- Adherence not affected by comorbidity score
- Diuretics lower for persistence and 2-year 80% adherence ($p < 0.001$ and $p < 0.01$, respectively) and for combined persistence/adherence (34.2% versus</td><td>General comments:
Analysis of pharmacy database

Quality assessment:
Overall rating: Good

Applicability:
- Pharmacy database does not capture clinical information that may influence choice of prescribed anti-hypertensive or explain reason for starting medication (e.g., CHF, not HTN) or for discontinuation of medication (e.g., formulary issues, not intolerance)
- Results not reported for persistence or adherence for single agent only to determine ACEI vs. ARB direct comparison</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Assessors of outcomes: No Was allocation concealment adequate?: NA Baseline/run-in period: NA Duration of treatment: NA Duration of post-treatment followup: 2 years	**Comorbidities (n [%]):** Chronic disease score (mean ± SD) 2.9 ± 2.7 **Recruitment setting:** Enrollees of Quebec provincial drug plan Inclusion criteria: **-** HTN diagnosis - On anti-HTN med, with first use occurring during index period - Covered by drug plan for entire study period Exclusion criteria: Used the anti-HTN drug in 12 months prior to index period	46.5%; p < 0.01) compared with other anti-HTN drugs **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Lacourciere, Belanger, Godin, et al., 2000 **#1591**	Geographical location: 8 centers in Canada Study dates: NR Funding source: Merck Interventions: - Losartan 50-100 mg daily (n = 52) - Enalapril 5-20 mg daily (n = 51) Dose titration/co-interventions: - Losartan: Start at 50 mg daily x 8 wks. If DBP > 85, then increase to100 mg daily. If DBP >85 at week 12, then add HCTZ 12.5 mg daily titrated to 25 mg until DBP ≤ 85 (could then add other BP meds to achieve goal, but not	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 103 - Began treatment: 102 - Completed treatment: 92 - Withdrawals/losses to followup: 11 Age: Mean: 58.5 Median: NR Range: NR **Sex (n [%]):** Female: 20 (19.4%) Male: 83 (80.6%) Race/ethnicity (n [%]): Caucasion: 99 (96%)	**1) Blood pressure:** Average of 3 seated trough clinic values (SD): SBP DBP Losartan: Pre: 163.3 ± 16.2 97.2 ± 6.3 Post (52 wk): 148.3 ± 17.1 86.8 ± 9.6 Enalapril: Pre: 157.7 ± 15.9 95.3 ± 4.8 Post (52 wks): 145.5 ± 18.2 84.4 ± 8.4 Clinic BP at other time points measured, but not reported. Also report 24-h ambulatory BP at 4 time	**General comments:** - Small study - No description of recruiting strategy or number of patients screened to generate study sample - Do not present complete data for many outcomes, only those that are statistically significant - 2 patients (1 in each group) excluded from analysis due to uncontrolled hypertension Quality assessment: Overall rating: Fair Comments: See above **Applicability:** - Placebo run-in limits assessment

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	specified by protocol) - Enalapril: Start at 5 mg daily x 4 wk. If DBP > 85, then increase to 10 mg daily. At week 8, if DBP still > 85, then increase to 20 mg daily. At week 12, if DBP still > 85, then add HCTZ 12.5 mg daily and titrate to 25 mg until DBP ≤ 85 (could then add other BP meds to achieve goal, but not specified by protocol) Patients with DBP > 100 at week 20 were discontinued from study. Early titration allowed in patients at week 4 if DBP > 105. Study design: RCT- parallel group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: 2-wk placebo run-in. Was preceded by 7-day wash out of previous HTN meds (14-day wash out of ACEIs) Duration of treatment: 52 wk Duration of post-treatment followup: NA	Asian: 3 (3%) Black: 1 (1%) **Baseline blood pressure:** Trough BP measured using standard mercury sphygmomanometer after 5 min rest; average of 3 measurements: Losartan / Enalapril SBP 162.3 ± 16.2 / 157.7 ± 15.9 DBP 97.2 ± 6.3 / 95.3 ± 4.8 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR (all diabetic) **Recruitment setting:** NR (seems like outpatient clinics) Inclusion criteria: - DM2 dx at age ≥ 30 - Sitting DBP 90-115 - Urinary albumin excretion 20-350 mcg/min Exclusion criteria: *There was a placebo run-in period. Didn't indicate how many were excluded by run-in. - Suspicion of renovascular disease - History of malignant htn (SBP>210 mmHg)	points during study (baseline, week 12, 28, and 52) – but only 5 of 8 sites did this. **2) Rate of use of a single antihypertensive agent for BP control:** Losartan group on monotherapy – 20/52 (38.5%) Enalapril group on monotherapy – 31/52 (59.6%) **3) Mortality:** No deaths **4) Morbidity:** No CV events **5) Safety:** Withdrawals due to AEs: Enalapril – 1 (cough) Losartan – 2 (1 w/ dyspnea and 1 w/ urticaria) **6) Specific adverse events:** Cough: Enalapril – 7 patients (14%) Losartan - 0 patients **7) Persistence/adherence:** NR **8) Lipid levels:** Total cholesterol difference at 52 wk compared to baseline (pre-/post- values NR): Losartan: 2.1% decrease Enalapril: 4.2% decrease P < 0.05 Also report limited data on LDL for losartan only and triglycerides for enalapril only. **9) Progression to type 2 diabetes:** NR	of discontinuation rates - Missing a great deal of data on the number of analyses performed and specific data; they seem to report selectively the statistically significant findings - Long list of exclusions for patients with CV comorbidities

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Stroke, TIA, or MI in previous 12 months - Significant heart conduction distubances or arrhythmia - Unstable angina - History of heart failure - Serum Cr ≥ 200 mmol/L - Serum potassium ≥ 5.5 mmol/L or ≤ 3.5mmol/L - Treatment with oral corticosteroids - Concomitant use of agents that may affect BP except B-blockers and nitrates - Drug or alcohol abuse - Pregnancy or breast feeding - Ineffective contraception	**10) Markers of carbohydrate metabolism/diabetes control:** HbA1c change at 52 wks compared to baseline (pre-/post- values NR): Losartan: + 0.006 Enalapril: + 0.0025 **11) LV mass/function:** NR **12) Creatinine/GFR:** GFR declined approx 9% in each group by week 52 (P < 0.001 for pre-/post- analysis). Values not given for GFR at 52 wk. **13) Proteinuria:** Urine albumin excretion based on average of 3 measurements: Losartan: Pre: 64.1 mcg/min (no SD given) Post (52 wk): 41.5mcg/min Enalapril: Pre: 73.9mcg/min Post (52 wk): 33.5 mcg/min P-value for pre-post was < 0.001 for both. No significant difference between treatments (no p-value given).	
Lacourciere, Neutel, Davidai, et al., 2006 **#287**	Geographical location: 81 U.S. and Canadian sites Study dates: Oct 1, 2002 to July 17, 2003 Funding source: NR	Number of patients: N = 812 - Screened for inclusion: 1998 - Eligible for inclusion: - Randomized: 812 - Began treatment: 812 - Completed treatment: 722 - Withdrawals/losses to followup: 90, 35 due to AEs, 12 due to lack	**1) Blood pressure:** Seated trough BP at 14 wk: Telmisartan / Ramipril / p-value SBP 139.6 / 143.4 / < 0.0000 DBP 88.7 / 92.0 / <	**General comments:** None Quality assessment: Overall rating: Fair Comments: - Patients and providers not

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Interventions: Forced titration of: - Ramipril 2.5 mg/5 mg/10 mg (n = 407) - Telmisartan 40 mg/80 mg/80 mg (n = 405) Doses were titrated after 2 weeks, then after 6 weeks, then again after 6 weeks Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: Yes Was allocation concealment adequate?: NR Baseline/run-in period: Screening 1-7 days; then patients previously treated with an ACEI, ARB, or diuretic underwent a 4-week run-in period, and all other enrollees underwent a 2-week run-in period with placebo Duration of treatment: 14 wk Duration of post-treatment followup: NR	of efficacy, 13 lost to followup, 14 "investigator decision", 18 patient decision (note: reported numbers do not total correctly) Age: Mean (SD): 52.5 ± 9.8 Median: NR Range: NR **Sex (n [%]):** Female: 269 (33.1%) Male: 543 (66.9%) Race/ethnicity (n [%]): 87.7% white (712) **Baseline blood pressure:** Seated trough BP measured by manual cuff sphygmomanometer: <u>Telmisartan</u> <u>Ramipril</u> SPB 153.9 ± 12.2 152.5 ± 12.8 DBP 99.7 ± 4.2 99.8 ± 4.3 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** Clinic setting Inclusion criteria: - Age ≥ 18 yr - Mild-moderate hypertension at baseline (mean DBP ≥ 95 and ≤	0.0001 SBP response at 14 wk (trough seated SBP < 140 mm Hg or reduction from baseline of ≥ 10 mm Hg): Telmisartan: 70.7% Ramipril: 62.7% p < 0.01 DBP response at 14 wk (trough seated DBP < 90 mm Hg or reduction from baseline of ≥ 10 mm Hg): Telmisartan: 60.5% Ramipril: 46.8% p < 0.01 ABPM outcomes also reported (primary) **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Severe AEs: Telmisartan: 15 (3. 8%) Ramipril: 30 (7.4%) Serious AEs: 14 patients (treatment group NR), none considered to be drug-related Withdrawals due to AEs: Telmisartan: 12 (3.0%) Ramipril: 23 (5.7%) **6) Specific adverse events:** AEs occurring at a rate of ≥ 1% and judged	blinded **Applicability:** - Significant number of limitations to inclusion in the study as evidence by number of screened patients to enrolled

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		109 mm Hg measured by manual cuff and 24-hr DBP > 85 mm Hg measured by ABPM [Spacelabs 90207] during the morning, daytime, and nighttime periods Exclusion criteria: - Mean seated SBP ≥ 180 or mean seated DBP ≥ 110 mm Hg during any visit of the placebo run-in or if they had secondary hypertension, CHF, stroke within 6 months, PTCA within 3 months, hemodynamically significant valvular heart disease, myocardial obstructive pathologic conditions, or clinical relevant arrhythmias - Night shift workers excluded - Excluded for relevant organ system disease (poorly controlled diabetes, significant hepatic, renal dysfunction, - Any hypersensitivity or reaction (including angioedema) to ACEI or ARB, history of non-compliance, substance abuse, sodium depletion, hypokalemia, or hyperkalemia, hereditary fructose intolerance, bililary tract obstruction	to be drug-related: <u>Telmisartan</u> <u>Ramipril</u> Peripheral edema 4 (1%) 0 Dizziness 6 (1.5%) 4 (1%) HA 4 (1%) 6 (1.5%) Cough 1 (0.2%) 33 (8%) **7) Persistence/adherence:** Withdrawals and reasons: Telmisartan: Adverse events (n = 12) Lack of efficacy (n = 7) Lost to follow-up (n = 5) Investigator' decision (n = 8) Patient decision (n = 12) Ramipril: Adverse events (n = 23) Lack of efficacy (n = 5) Lost to follow-up (n = 8) Investigator' decision (n = 6) Patient decision (n = 6) **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Larochelle, Flack, Marbury, et al., 1997 **#1592**	Geographical location: NR; investigators from Canada, Brazil, S. Africa, US Study dates: NR Funding source: Bristol-Myers Squibb Interventions: - Irbesartan (n = 121) 150 mg once daily - Enalapril (n = 61) 20 mg once daily At end of 1 week if seated DBP was ≥ 90, then titration of irbesartan to 300 mg, enalapril to 40 mg After week 4, if seated DBP was ≥ 90, open-label once-daily adjunctive antihypertensive medications were added (HCTZ 25-50 mg/day, followed by long-acting nifedipine 30-60 mg.day and/or atenelol 50-100 mg/day) Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: Diuretics	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 182 - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR Age: Mean (SD): NR Median: NR Range: NR **Sex (n [%]):** Female: 72 (40%) Male: 110 (60%) Race/ethnicity (n [%]): White: 98 (54%) Black: 58 (32%) Other: 26 (14%) **Baseline blood pressure:** Trough-seated DBP 24 ± 3 hr after ingestion of previous day's medication <u>Irbesartan</u> <u>Enalapril</u> SBP 176.7 ± 17.8 175.4 ± 15.2 DBP 119.2 ± 3.9 119.0 + 3.3 **Concurrent medications (n [%]):** NR (though see Exclusion criteria) **Comorbidities (n [%]):** NR	**1) Blood pressure:** Reduction in trough seated DBP from baseline at 12 wk: Percentage of patients "normalized" (trough seated DBP < 90 mm Hg) at 12 wk: Irbesartan: 59% Enalapril: 57% p = 0.97 Percentage of "responders" (trough seated DBP normalized or reduced ≥ 10 mm Hg from baseline) at 12 wk: Irbesartan: 100% Enalapril: 98% p = 0.97 **2) Rate of use of a single antihypertensive agent for BP control (%):** On monotherapy at 12 wk: Irbesartan: 9% Enalapril: 7% Also taking HCTZ: Irbesartan: 24% Enalapril: 18% Taking ≥ 3 adjunctive meds: Irbesartan: 67% Enalapril: 75% **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** No changes in lab parameters, ECG findings or physical exam findings	**General comments:** None Quality assessment: Overall rating: Fair Comments: - Setting of study; no description (country? system? center selection? study clinicians?) - No data regarding numbers of patients screened or eligible for inclusion - Raw numbers not reported, only percentages **Applicability:** - Patient compliance not assessed

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	withdrawn for at least 3 days, other anti-hypertensives for at least 24 hr. Patients with seated DBP > 115-130 entered to double-blind phase Those with DBP ≤ 115 entered a single-blind placebo lead-in period of up to 7 days Duration of treatment: 12 weeks Duration of post-treatment followup: NA	(though see Exclusion criteria) **Recruitment setting:** NR Inclusion criteria: - Seated diastolic BP 115-130 - Men and surgically sterile or post-menopausal women > 18 yr - Signed an informed consent Exclusion criteria: - Concomitant disease that would present safety hazards - Concomitant medications known to affect BP - Patients with seated BP < 115 at day 7 of wash-out period	Patients with AEs (%): Irbesartan: 55% Enalapril: 64% **6) Specific adverse events (%):** Irbesartan / Enalapril Headache 17.4% / 19.7% Dizziness 9.1% / 18.0% Cough 2.5% / 13.1%* URI 13.1% / 9.9% *p= 0.007 **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Mackay, Pearce, and Mann, 1999 **#1594**	**Geographical location:** United Kingdom **Study dates:** Immediate post-marketing period for 4 drugs, through 6 mo followup Enalapril (1985) Lisinopril (1988) Perindopril (1990) Losartan (1995) **Funding source:** Pharmaceutical companies **Interventions:** - Enalapril (dose NR; n = 15,361 analyzed) - Lisinopril (dose NR; n = 12,438 analyzed) - Perindopril (dose NR; n = 9089 analyzed) - Losartan (dose NR; n = 14,522 analyzed) **Study design:** Prospective cohort **Blinding:** - Patients: No - Providers: No - Assessors of outcomes: No **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** Up to 6	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: NR - Completed treatment: 51,410 analyzed - Withdrawals/losses to followup: NR (except for withdrawals due to cough) **Age:** Mean (SD): 61.9 (~ 13) Median: NR Range: NR **Sex (n [%]):** Female: 28,215 (55.7%) Male: 22,478 (44.3%) **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** Cardiac failure 8.8% **Recruitment setting:** Initial post-marketing surveillance cohort **Inclusion criteria:** All patients dispensed incident prescriptions for each drug in the immediate post-marketing period in England; and their prescribing	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** Patients with cough: Drug / Pts w/ cough / Rate per 1000 pt-mo / 95% CI Enalapril / 86 / 3.9 / 3.1 to 4.8 Lisinopril / 270 / 14 / 13 to 16 Perindopril / 210 / 16 / 14 to 19 Losartan / 64 / 3.1 / 2.4 to 4.0 Rate ratios for cough, day 8 to 60, compared to losartan: Drug / RR crude / RR adj for age and sex / 95% CI Enalapril / 1.3 / 1.5 / 1.2 to 2.2 Lisinopril / 4.6 / 4.8 / 3.6 to 6.5 Perindopril / 5.3 / 5.7 / 4.2 to 7.6 Rate ratios for cough; females compared with males Drug / RR crude / RR adj for age / 95% CI Enalapril / 1.5 / 1.4 / 0.8 to 2.5	**General comments:** - Authors suggest most cough associated with losartan is due to carry over from ACEI , since most patients put on losartan were switched for ACEI-related cough **Quality assessment:** Overall rating: Poor Comments: - Non-concurrent time periods for assessment of different drugs - Assembly of cohort not well-described **Applicability:** - Assessment in first few months of use of new drug products suggests that prescribing patterns may no longer be the same

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	mo **Duration of post-treatment followup:** Up to 6 mo	general practitioners were mailed a questionnaire **Exclusion criteria:** NR, but presumably failure of GP to return questionnaire	<table><tr><td>Lisinopril</td><td>1.6</td><td>1.6</td><td>1.2 to 2.2</td></tr><tr><td>Perindopril</td><td>1.6</td><td>1.6</td><td>1.2 to 2.1</td></tr><tr><td>Losartan</td><td>1.7</td><td>1.5</td><td>0.8 to 2.6</td></tr></table> **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Malacco, Omboni, Volpe, et al., 2010 **#2217**	**Geographical location:** 102 centers in Italy **Study dates:** NR **Funding source:** Laborati Guidotti and Malesci Istituto Farmacobiologico. **Interventions:** 1. Olmesartan medoxomil. Initial dose 10 mg/day. 2. Ramipril. Initial dose 2.5 mg/day. In both arms, dose was doubled in weeks 2-6 if SBP ≥ 140 or DBP ≥ 90 mm Hg in non-diabetic patients, and if SBP ≥ 130 or DBP ≥ 80 mm Hg in diabetic patients, up to a maximum of 40	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: 1242 - Randomized: 1102 - Began treatment: 1102 - Completed treatment: 980/1102 (89%) - Withdrawals/losses to followup: 122/1102 (11%). 1081/1102 (98%) patients included in intention-to-treat analysis (olmesartan n = 542; ramipril n = 539) **Age:** Mean (SD): Olmesartan: 71.7 (5.0) Ramipril: 72.0 (5.0) Median: NR	**1) Blood pressure:** Change in sitting SBP at 12 weeks, mm Hg (95% CI): Olmesartan: 17.8 (16.8, 18.9) Ramipril: 15.7 (14.7, 16.8) p = 0.01 Change in sitting DBP at 12 weeks, mm Hg (95% CI): Olmesartan: 9.2 (8.6, 9.8) Ramipril: 7.7 (7.1, 8.3) p = 0.01 Subgroup analyses also reported for ages 65-69 and > 70 years Change in ambulatory SBP at 12 weeks, last 6 hours, mm Hg (95% CI): Olmesartan: 10.5 (11.8, 9.0) Ramipril: 7.3 (8.7,5.9) p = 0.01	**General comments:** None **Quality assessment:** Overall rating: Good Comments: - Well-designed and reported study - Funded by pharmaceutical company **Applicability:** - Conducted in Italy - Monotherapy only

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	mg for olmesartan and 10 mg for ramipril. **Were additional anti-hypertension medications allowed:** No (by inference, no additional anti-hypertension medications allowed) **If Yes to above, was this done:** NA **Study design:** RCT, parallel-group. Non-inferiority design. **Blinding:** - Patients: Yes (by inference) - Providers: Yes (by inference) - Assessors of outcomes: Yes (by inference) **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 2-week run-in (authors used the term "washout") period with placebo prior to the 12-week RCT phase for patients previously on anti-hypertension medication **Washout period(s):** NA **Duration of treatment:** 12 weeks **Duration of post-treatment followup:** NA	Range: NR **Sex (n [%]):** Olmesartan: Female: 264 (49%) Male: 278 (51%) Ramipril: Female: 265 (49%) Male: 274 (51%) **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Sitting, resting BP, with mean of 3 readings, 2 minutes apart, reported. All readings taken in the morning, approximately 24 hours after last drug intake. Also 24-hour ambulatory BP monitoring at randomization and final visit in a subgroup of patients (n = 630). Sitting SBP at baseline, mm Hg (SD): Olmesartan: 156 (10) Ramipril: 156 (10) Sitting DBP at baseline, mm Hg (SD): Olmesartan: 91 (7) Ramipril: 90 (7) **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** 20% with diabetes	Change in ambulatory DBP at 12 weeks, last 6 hours, mm Hg (95% CI): Olmesartan: 6.1 (7.0, 5.3) Ramipril: 45. (5.3, 3.6) p = 0.01 **2) Rate of use of a single antihypertensive agent for BP control:** Proportion normalized on monotherapy at 12 weeks: Olmesartan: 52.6% Ramipril: 46.0% p = 0.03 **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** A total of 136 (12.3%) patients reported AEs (75 in the olmesartan and 61 in the ramipril groups), for an overall number of 175 AEs (98 in the olmesartan and 77 in the ramipril groups). 33 patients (3.0%) were withdrawn from the study because of AEs (14 in the olmesartan and 19 in the ramipril groups). **6) Specific adverse events:** Cough, N (%): Olmesartan: 2 (0.4%) Ramipril: 13 (2.4%) **7) Persistence/adherence:** 122 (11%) patients did not complete the protocol for the following reasons: consent withdrawal (n = 42); lost to followup (n = 22); adverse events (n = 20); protocol violation (n = 14); lack of efficacy (n = 11); lack of compliance to study procedures (n =	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			8); other (n = 5)	
		Recruitment setting: 102 outpatient clinics and centers in Italy	**8) Lipid levels:** NR	
			9) Progression to type 2 diabetes: NR	
		Inclusion criteria: - Age 65-89 - Outpatient - Grade 1 or 2 HTN - DBP between 90-109 or SBP between 140-179 mm Hg after 2 weeks of washout with placebo	**10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR	
			12) Creatinine/GFR: NR	
		Exclusion criteria: NR	**13) Proteinuria:** NR	
Malacco, Santonastaso, Vari, et al., 2004 **#1595**	**Geographical location:** 88 outpatient centers in Italy **Study dates:** NR **Funding source:** Novartis **Interventions:** - Valsartan 160 mg (n = 604) - Lisiniopril 20 mg (n = 609) Dose titration and co-interventions: No dose titration; HCTZ 12.5 mg added at 4 wk for non-responders (SBP > 150 or decrease < 20 [if SBP < 180] or decrease < 30 [if SBP ≥ 180]) **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: NR	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 1213 - Began treatment: 1213 - Completed treatment: 1100 - Withdrawals/losses to followup: 113 (32 due to AEs, other causes NR) **Age:** Mean (SD): 54.1 (10.1) Median: NR Range: 28-78 **Sex (n [%]):** Female: 578 (48%) Male: 635 (52%) **Race/ethnicity (n [%]):** White: 100% **Baseline blood pressure:** Trough seated BP measured 3 times after 5-min rest using	**1) Blood pressure:** Mean BP (± SD) at 16 wk (ITT population): Valsartan (n = 594) / Lisinopril (n = 591) SBP: 137.2 ± 13.3 / 136.8 ± 12.2 DBP: 83.9 ± 7.1 / 83.7 ± 7.0 Rates of BP control (SBP ≤ 150 or decrease ≥ 20 [if baseline SBP < 180] or ≥ 30 [if baseline SBP ≥ 180]): Valsartan: 428 (82.6%) Lisinopril: 409 (81.6%) p = NS Also reported: Mean BP at 16 wk for per-protocol population Mean reductions in BP vs. baseline (ITT and per-protocol populations) **2) Rate of use of a single antihypertensive agent for BP control:** Valsartan: 79.3%	**General comments:** None **Quality assessment:** Overall rating: Good **Applicability:** - Setting/recruitment/selection NR - Exclusion criteria strict and vague

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Assessors of outcomes: Yes **Was allocation concealment adequate?:** Yes **Baseline/run-in period:** 2-wk placebo run-in **Duration of treatment:** 16 wk **Duration of post-treatment followup:** NA	mercury sphygmomanometer; mean of 3 readings used Mean baseline values (± SD): Valsartan (n = 594) / Lisinopril (n = 591) SBP 167.4 ± 10.2 / 167.2 ± 9.5 DBP 99.3 ± 4.2 / 99.1 ± 4.3 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** - Age ≥ 18 yrs - Mild to severe HTN (SBP 160-220 and DBP 95-110) **Exclusion criteria:** - Malignant HTN - TIA, CVA, or MI within 6 months - Secondary HTN - CHF - Clinically relevant arrhythmia - Clinically significant valvular heart disease - Liver disease - Hyperkalemia - Serum creatinine > 1.5 times normal - Type 1 diabetes - Type 2 diabetes with poor glucose control or neuropathy - Known hypersensitivity to ARB,	Lisinopril: 78.7% **3) Mortality:** No deaths occurred during trial **4) Morbidity:** NR **5) Safety:** Any drug-related AE: Valsartan: 31/604 (5.1%) Lisinopril: 65/609 (10.7%) p = 0.001 Severe AEs: Valsartan: 3/604 (< 0.5%) Lisinopril: 3/609 (< 0.5%) Withdrawals due to AEs: Valsartan: 9/604 (1.5%) Lisinopril: 23/609 (3.8%) p = 0.01 **6) Specific adverse events:** Drug-related AEs: |	Valsartan (n = 604)	Lisinopril (n = 609)
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Cough*	6 (1%)	44 (7.2%)
Headache	4 (0.7%)	9 (1.5%)
Vertigo	4 (0.7%)	1 (0.2%)
Asthenia	3 (0.5%)	4 (0.7%)
Palpitations	2 (0.3%)	2 (0.3%)
Hypotension	1 (0.2%)	3 (0.5%)	 **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		ACEI, or thiazides - Pregnant, possibly pregnant, or breastfeeding women - Women of childbearing age not using birth control	**10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Malde, Regalado, and Green-berger, 2007 **#223**	**Geographical location:** Chicago, IL **Study dates:** Jan 1991-May 2004 **Funding source:** Ernest S. Bazley Grant to Northwestern Memorial Hospital and Northwestern University **Interventions:** Routine use of ACEI or ARB prior to development of angioedema and presentation to ER **Were additional anti-hypertension medications allowed:** NR **Study design:** Other – retrospective cohort **Blinding:** - Patients: NA - Providers: NA - Assessors of outcomes: NA **Was allocation concealment adequate?:** NA	**Number of patients:** N = 64 - Screened for inclusion: 278 - Eligible for inclusion: 64 - Randomized: NA - Began treatment: NA - Completed treatment: NA - Withdrawals/losses to followup: NA **Age:** Mean (SD): 60.2 Median: 59 Range: 32–92 **Sex (n [%]):** Female: 38 (60%) Male: 26 (40%) **Race/ethnicity (n [%]):** AA: 44 (69%) White: 15 (23%) Hispanic: 2 (3%) Other: 3 (5%) **Baseline blood pressure:** NR **Concurrent non-hypertension medications (n [%]):** N (%) NSAID or aspirin: 24 (38%) Cyclo-oxygenase 2 inhibitor: 4 (6%)	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** Thirteen patients (20%) were admitted to the medical intensive care unit. Of these, 2 were intubated, and no patients required a tracheostomy. There were no fatalities. **5) Safety:** NR **6) Specific adverse events:** Angioedema: ACEI (n = 61), ARB (n = 3) Women 60% African American 69% Caucasian 23% Hispanics 2% **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR	**General comments:** Multiple indications for ACEI or ARB **Quality assessment:** Overall rating: Fair Comments: Limited to single center **Applicability:** - Not all study pts had HTN - Half of study population had other concomitant med that could have also caused angioedema

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Baseline/run-in period: NA **Duration of treatment:** Varied, range 1 day to 10 years, mean 1.8 years Time to angioedema presentation after starting ACEI or ARB Mean for 51 patients (years) 1.8 1 month 13 (25%) First week 6 (12%) 1 month to 1 year 18 (35%) 1 year 14 (28%) **Duration of post-treatment followup:** NA	Opiate: 3 (5%) **Comorbidities (n [%]):** HTN 19 (30%) HTN and DM 9 (14%) CAD or CHF 10 (16%) Unspecified 26 (41%) **Recruitment setting:** Emergency room **Inclusion criteria:** Adverse event due to ACEI or ARB consisting of angioedema, urticaria, or anaphylaxis **Exclusion criteria:** Other types of adverse events	**11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Mallion, Bradstreet, Makris, et al., 1995 **#1596**	**Geographical location:** Multicenter, with sites in Italy, Costa Rica, France, Switzerland, New Zealand, Germany, Austria, The Netherlands, and Portugal **Study dates:** NR **Funding source:** NR (multiple authors from Merck) **Interventions:** - Losartan 50-100 mg (n = 109) - Captopril 50-100 mg (n = 54) Dose titration and co-interventions: Patients started on 50 mg and titrated up to 100 mg if BP not controlled (DBP 90-115 mm Hg) at 6 wk; no co-interventions	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 163 - Began treatment: 163 - Completed treatment: 142 - Withdrawals/losses to followup: 21 (15 due to AEs, 3 lost to followup, 3 not described) **Age:** Mean (SD): 54.1 Median: NR Range: NR **Sex (n [%]):** Female: 63 (39%) Male: 100 (61%) **Race/ethnicity (n [%]):** Caucasian: 145 (89%)	**1) Blood pressure:** Mean BP at 12 wk: Losartan (n = 109) / Captopril (n = 51) SBP: 149.8 (20.3) / 151.4 (16.4) DBP: 93.9 (9.3) / 97.9 (9.2) Adjusted* mean change in BP at 12 wk: Losartan (n = 109) / Captopril (n = 51) / P-value SBP: -9.1 / -7.9 / NS DBP: -9.1 / -5.7 / ≤ 0.01 *Adjusted for baseline BP BP response rates at 12 wk (DBP < 90 or DBP ≥ 90 with reduction of ≥ 10 from baseline):	**General comments:** - Patients withdrawn if DBP not ≥ 95 during placebo run-in period resulting in some potential exclusions - Primary outcome was change in DBP, but one wonders if this was established a priori since it was the only significant BP change during the study. - Randomization stratified by degree of hypertension (mild vs. moderate) **Quality assessment:** Overall rating: Fair Comments: - Numbers of screened and eligible patients NR

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	allowed **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes **Was allocation concealment adequate?:** Yes – details not specified **Baseline/run-in period:** 4-wk placebo run-in **Duration of treatment:** 12 wk **Duration of post-treatment followup:** 1 wk without study drugs to determine rebound HTN	Oriental: 2 (1%) Latin American: 9 (6%) Black: 4 (2%) Asian: 3 (2%) **Baseline blood pressure:** Trough seated BP measured 3 times at 1-min intervals after 5 min rest (instrument not specified); average of 3 readings used Losartan / Captopril SBP 159.3 (16.8) / 159.4 (16.2) DBP 103.1 (5.3) / 103.7 (5.5) **Concurrent medications (n [%]):** - Non-study BP meds not permitted - Allowed acetaminophen, aspirin, NSAIDs **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** - Age ≥ 18 yr - Mild-to-moderate essential HTN (mean sitting DBP 90-115 before placebo run-in, then 95-115 after 2 and 4 wk on placebo) **Exclusion criteria:** - Known hypersensitivity/ contraindication (including angioedema, cough) to captopril	Losartan: 55/109 (50.5%) Captopril: 15/51 (29%) $p \leq 0.05$ Subgroup analyses (no formal statistical testing done): Mean reduction in DBP at 12 wk, age < 65 vs. ≥ 65: Age < 65 / Age ≥ 65 Losartan DBP -9.4 / -8.1 Captopril DBP -5.1 / -7.7 Sex "not a significant demographic factor, although DBP reductions were slightly higher in men at all time-points within both treatment groups" **2) Rate of use of a single antihypertensive agent for BP control:** NA (no other antihypertensive meds allowed) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Losartan (n [%]) / Captopril (n [%]) ≥ 1 AE 42 (38.5%) / 20 (37.0%) Withdrawals due to AEs 10 (9.2%) / 5 (9.3%) Drug-related AEs 16 (14.7%) / 10 (18.5%)	**Applicability:** - Minimal racial diversity (89% Caucasian) - Recruitment setting(s) not described - Minimal comorbidities in study population of hypertensive patients

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		or other ACEI - Significant cardiovascular, cerebrovascular, renal/ hepatic disease - Secondary or malignant HTN - Recent MI - Serum K <3.5 or > 5.5 mmol/L or other laboratory values outside of the normal ranges - Women of child-bearing age if not surgically sterile or using effective contraception	**6) Specific adverse events:** AEs occurring in > 4% of patients in either group: Losartan (n = 109) n (%) / DRn (%) / DR Captopril (n = 54) n (%) / DRn (%) / DR Headache: 8 (7.3) 2 / 4 (7.4) 3 Nausea: 6 (5.5) 1 / 2 (3.7) 2 Dizziness: 4 (3.7) 1 / 3 (5.6) 2 URI: 5 (4.6) 0 / 0 DR = # AEs considered to be drug-related **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Malmqvist, Kahan, and Dahl, 2000 **#1597**	**Geographical location:** 56 centers, locations not reported **Study dates:** NR **Funding source:** Astra Hässle AB **Interventions:**	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: 512 - Randomized: 429 - Began treatment: 429 - Completed treatment: 404 - Withdrawals/losses to followup: 26 (17 due to AEs, 9 for other reasons)	**1) Blood pressure:** Mean post-treatment BP values NR Mean change in seated trough BP from baseline to 12 wk (no variance data reported): Candesartan / Enalapril SBP -19 / -13	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: - Mean baseline and post-treatment BP values NR

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Candesartan 8 to 16 mg (n = 140) - Enalapril 10 to 20 mg (n = 146) - HCTZ 12.5 to 25 mg (n = 143) Dose titration/co-interventions: Higher doses used if DBP > 90 mm Hg after 6 wk; no co-interventions **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes (double-dummy) - Providers: NR - Assessors of outcomes: Yes **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 3- to 6-wk placebo run-in **Duration of treatment:** 12 wk **Duration of post-treatment followup:** NA	**Age:** Mean: 57.7 Median: Range: 40 to 70 **Sex (n [%]):** Female: 100% Male: 0% **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Trough seated BP measured in duplicate, with an interval of at least 1 min, after patient rested in seated position for 5 min Mean baseline values NR **Concurrent medications (n [%]):** Non-study medication that would affect BP not allowed; no changes permitted to hormone replacement therapy **Comorbidities (n [%]):** History of habitual smoking: 9% Estrogen replacement: 22% **Recruitment setting:** NR **Inclusion criteria:** - Women age 40-69 yr - Untreated or treated primary hypertension (seated DBP 95-115) from a mean of 2 measurements at the end of placebo run-in period	DBP -11 -9 Mean difference between treatments (candesartan vs. enalapril) in change in seated trough BP from baseline to 12 weeks: Mean diff 95% CI P-value SBP -5.5 -9.1 to -1.9 < 0.01 DBP -2.2 -3.9 to -0.5 = 0.01 BP control rates (seated DBP ≤ 90 mm Hg) at 12 wk: Candesartan: 60% Enalapril: 51% p = NS **2) Rate of use of a single antihypertensive agent for BP control:** No other antihypertensives permitted **3) Mortality:** NR **4) Morbidity:** No difference in Psychological General Well-Being, McMaster Overall Treatment Evaluation Questionnaire (data not reported) **5) Safety:** Any AEs: Candesartan: 60% Enalapril: 67% 10 serious AEs were reported (treatment groups not specified); none assessed as related to study drug 17/429 randomized patients (4%) withdrew	**-** Patients withdrawn from study if mean seated SBP > 200 mm Hg or DBP > 110 mm Hg on > 2 occasions in 1 wk **Applicability:** - High loss during placebo run-in period (62/512 initially enrolled) - 100% women - Exclusion of patients who did not respond to therapy (seated SBP > 200 mm Hg or DBP > 110 mm Hg on > 2 occasions in 1 wk) means that analyzed population is a selected group of those who did respond; leads to bias

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			due to AEs; treatment groups not specified	
		Exclusion criteria: - Secondary or malignant hypertension - Seated SBP > 200 mm Hg - MI, stroke, coronary bypass surgery, TIA within prior 6 mo - Angina, aortic/mitral valve stenosis, heart failure, or arrhythmia - Insulin-treated diabetes - Gout - Severe concomitant disease that may interfere with assessment - Any condition associated with poor compliance (e.g., drug or alcohol abuse)	**6) Specific adverse events:** Number of patients (%): Respiratory infection: Candesartan 12 (8), Enalapril 7 (5) Fatigue: 11 (8), 7 (5) Headache: 10 (7), 27 (19) Dizziness: 6 (4), 10 (7) Cough: 0 (0), 19 (13) Palpitations: 5 (4), 0 (0) **7) Persistence/adherence:** Compliance (defined as amount of prescribed medication taken) was between 75 and 125% in all but 2 patients; not reported by treatment group **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Marentette, Gerth, Billings, et al., 2002 **#1598**	**Geographical location:** Saskatchewan, Canada (database including > 90% of provincial residents) **Study dates:** Jan 1994-Dec 1998	**Number of patients:** - Screened for inclusion: 51,029 - Eligible for inclusion: 46,458 - Randomized: NA - Began treatment: NA - Completed treatment: NA - Withdrawals/losses to followup:	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR	**General comments:** - Relatively small number of patients in ARB subgroup **Quality assessment:** Overall rating: Fair

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		NA		Comments:
	Funding source: Merck Frosst Canada, Ltd.		**4) Morbidity:** NR	- Non-random allocation to drugs - No data on comparability of patients on ACEIs versus ARBs
		Age (ARBs and ACEIs):		
		Mean: 58	**5) Safety:** NR	
	Interventions:	Median: NR		- Funded by pharmaceutical company
	Number of patients with data for at least 180 days:	Range: 1-85	**6) Specific adverse events:** NR	
	ARBs (n = 267)	**Sex (ARBs and ACEIs; %):**	**7) Persistence/adherence:**	**Applicability:**
	ACEIs (n = 7466)	Female: 48.8%	Sample sizes at various timepoints:	- Study period soon after introduction of ARBs; early use may not reflect current use patterns
	Beta-blockers (n = 4295)	Male: 51.2%		
	CCBs (n = 3200)		ARBs ACEIs	
	Diuretics (n = 9623)	**Race/ethnicity (n [%]):** NR	180 days	
	Alpha-blockers (n = 731)		267 7466	
	Alpha-agonists (n = 575)	**Baseline blood pressure:** NR	360 days	
	Vasodilators (n = 25)		170 6539	
	Mixed classes (more than 1 class concurrently or sequentially during study period; n = 20,276)	**Concurrent medications (n [%]):**	540 days	
		NR	44 5699	
			720 days	
			3 4826	
	Study design:	**Comorbidities (n [%]):**		
	Retrospective cohort study	NR	Small ARB sample explained by fact that ARBs not listed in provincial formulary until March 1996.	
	Blinding:	**Recruitment setting:**		
	- Patients: No	Population-based prescription drug database	Patient classified as persistent at a given period of observation (180, 360, 540, or 720 days) if patient filled at least one prescription within 90 days of the end of the given period and within 90 days of the end of each prior interval.	
	- Providers: No			
	- Assessors of outcomes: No			
		Inclusion criteria:		
	Was allocation concealment adequate?: NA	- ICD-9 code diagnosis of hypertension (401, 402, 403, 404, or 4-digit codes included in these categories)		
	Baseline/run-in period: NA			
		- At least 1 antihypertensive prescription during first 4.5 yr of study period	Extrapolating from Figure 2, persistence was:	
	Duration of treatment: NR		ARBs ACEIs	
		- No antihypertensive prescription in the 12 mo before the first prescription	180 days	
	Duration of post-treatment followup: Patients followed for minimum of 180 days to a maximum of 720 days		87% 75%	
			360 days	
			85% 65%	
		Exclusion criteria: None specified	540 days	
			- 60%	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			720 days - 55% When considering all drug classes, persistence was higher for males and for older ages. Persistence was reported by age for ACEIs (but not ARBs): 1-47 yr: 71.7% 48-57: 76.1% 58-66: 74.5% 67-74: 76.5% 75-95: 77.0% Note: "Persistence" includes combinations and switches; in essence, what is being modeled is failure to discontinue. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Matsuda, Hayashi, and Saruta, 2003 **#1599**	**Geographical location:** Honjo, Ashikaga, Tochigi, Japan **Study dates:** 1998-1999 **Funding source:** NR **Interventions:**	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 52 - Began treatment: 52 - Completed treatment: 52 - Withdrawals/losses to followup: 0	**1) Blood pressure:** Mild proteinuria Mod proteinuria SBP ACE ARB Baseline 148±3 154±4 152±4 150±3 12 wk 135±3 137±3 134±4 137±4	**General comments:** - All data were presented to compare subgroups with mild and moderate proteinuria with regard to effect of ACEI versus ARB **Quality assessment:** Overall rating: Poor

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- ACE group - perindopril 2 mg or trandolapril 1 mg (dose titrated to achieve SBP < 135 and DBP < 85) (n = 27) - ARB group – losartan 25 mg or candesartan 4 mg (dose titrated to achieve SBP < 135 and DBP < 85) (n = 25) **Study design:** RCT, parallel-group **Blinding:** - Patients: NR - Providers: NR - Assessors of outcomes: NR **Was allocation concealment adequate?:** NR **Baseline/run-in period:** NR **Duration of treatment:** 48 weeks **Duration of post-treatment followup:** NR	**Age:** Mean (SD): 52 Median: NR Range: NR **Sex (n [%]):** Female: 23 (44%) Male: 29 (56%) **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Average of 2 measurements taken after 5 min in sedentary position (seated or supine NR) Mild proteinuria / Mod proteinuria ACE n = 13 / ARB n = 13 / ACE n = 14 / ARB n = 12 S 148 ± 3 / 154 ± 4 / 152 ± 4 / 150 ±3 D 86 ± 5 / 86 ± 3 / 90 ± 3 / 89 ± 3 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** Outpatient clinic **Inclusion criteria:** - Hypertension (SBP > 140 and/or DBP > 90 mmHg) - Proteinuria (> 0.3 g/24 hr)	24 wk 132±4 NR 120±3 NR 48 wk 131±4 NR 124±3 NR Mild proteinuria Mod proteinuria DBP ACE ARB ACE ARB Baseline 86±5 86±3 90±3 89±3 12 wk 76±4 71±2 78±3 79±3 24 wk 80±3 NR NR NR 48 wk 74±4 NR NR NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR	Comments: - Poorly described methods regarding washout, co-interventions, dose titration - Position of BP measurement not described - No data on safety/adverse events **Applicability:** - Patient ethnicity not described, but likely all Japanese

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Serum creatinine level < 265 μmol/L or creatinine clearance > 30 mL/min/1.72 m^2 **Exclusion criteria:** - Diabetic nephropathy - Polycystic kidney disease - Chronic pyelonephritis	**11) LV mass/function:** NR **12) Creatinine/GFR:** "Neither ACE-I nor ARB had any effect on creatinine clearance" **13) Proteinuria:** No change in patients with mild proteinuria. In patients with moderate proteinuria, ACEI reduced proteinuria by 44 ± 6% (from 2.7 ± 0.5 to 1.5 ± 0.4 g/d; p < 0.05, n = 14) at 12 wks and 54 ± 7% at 48 wk (1.2 ± 0.2 g/d) ARB caused a 23 ± 8% decrease (from 2.7 ± 0.4 to 2.0 ± 0.4 g/d, p > 0.2, n = 12) at 12 wk (p < 0.05 versus ACEI) and 41% at 48 wk (p > 0.5 versus ACEI)	
Mazzaglia, Mantovani, Sturken-boom, et al., 2005 **#1600**	**Geographical location:** Italy **Study dates:** 2000-2001 **Funding source:** Pfizer Italia **Interventions:** A single antihypertensive in one of the following classes: - α-blockers (n = 662) - Diuretics (n = 2177) - β-blockers (n = 1780) - Calcium channel blockers (CCBs, n = 2700) - ACE inhibitors (n = 4602) - ARBs (n = 1382) **Study design:** Retrospective cohort study	**Number of patients:** Of 409,724 in the Health Search Database, 24,540 were newly diagnosed with hypertension; of these, 13,303 satisfied inclusion criteria (4967 did not receive antihypertensive therapy within 90 days of diagnosis, 6270 were started on combination therapy) **Age (ACEI/ARB):** Mean (SD): 66.0 (12.8)/64.0 (12.6) Median: NR Range: NR **Sex (ACEI/ARB; n [%]):** Female: 2484 (54.0%)/770 (55.7%) Male: 2118 (46.0%)/612 (44.3%)	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** See below, under Persistence/adherence **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Patients classified into one of the following groups: Continuers: Patients continuing the first-line medication for at least 1 yr; Combiners: Patients receiving an additional	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: - Cohort study, requiring multivariate adjustment to make groups more comparable **Applicability:** - Reflects Italian practice patterns and study population

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Blinding: NA **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** 365 days **Duration of post-treatment followup:** NA	**Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Average of last 2 separate measurements made by physicians within 3 mo before index date; method of assessment not specified ACEI ARB SBP 153.1 ± 19.1 153.2 ± 18.6 DBP 90.1 ± 10.6 90.6 ± 10.2 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** ACE ARB CAD 179 (3.9) 54 (4.0) HF 45 (0.98) 14 (1.01) DM 564 (12.3) 101 (7.3) Stroke 141 (3.1) 43 (3.1) Dyslip 415 (9.0) 220 (8.7) COPD 244 (5.3) 85 (6.2) Prostate 218 (4.7) 53 (3.8) 2+ comor-bidities 479 (10.4) 129 (9.3) **Recruitment setting:** Primary care clinics engaged in the Health Search Database **Inclusion criteria:**	type of antihypertensive drug and continuing the initial medication; Switchers: Patients changing from the first-line to another antihypertensive class and discontinuing the initial treatment; Discontinuers: Patients stopping the first-line therapy without having another antihypertensive prescription during followup. | | ACEI | ARB | |---|---|---| | Continuers | 23.3% | 25.2% | | Combiners | 26%* | 25%* | | Switchers | 10%* | 8%* | | Discontinuers | 40%* | 42* | * Estimates based on Figure 1; values not reported in text or tables Adjusted hazard ratio for discontinuation = 0.5 (95% CI 0.47 to 0.54) for ACEI, and 0.44 (0.41 to 0.48) for ARB. Adjusted hazard ratio for combining = 1.45 (1.29 to 1.64) for ACEI, and 1.35 (1.16 to 1.57) for ARB. (Adjustment included age, sex, baseline BP, comorbidities, and family history) **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Newly diagnosed hypertensives (ICD-9: 401-404, 437.2) - Age ≥ 35 yr during 2000-1 - Registered with one of the participating GPs for at least 1 yr before entry into the study - Received at least one antihypertensive medication within 3 mo of diagnosis **Exclusion criteria:** - Received antihypertensive drugs within 6 months prior to index date - Less than 365 days of valid follow-up after entry to the cohort - Received one-pill combination therapy or multiple pill medications as first-line therapy	**13) Proteinuria:** NR	
McInnes, O'Kane, Istad, et al., 2000 **#1601**	**Geographical location:** Multicenter: Glasgow, UK; Oslo, Norway; Oula, Finland; Oude Wetering, The Netherlands **Study dates:** NR **Funding source:** Astra Hassle **Interventions:** - Candesartan cilexetil 8 mg + HCTZ 12.5 mg (n = 237) - Lisinopril 10 mg + HCTZ 12.5 mg (n = 116) No dose titration; no co-interventions **Study design:** RCT, parallel-group	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: 418 - Randomized: 355 - Began treatment: 353 - Completed treatment: 286 - Withdrawals/losses to followup: 67 **Age:** Mean (SD): 57.5 ± 9.7 Median: NR Range: NR **Sex (n [%]):** Female: 158 (45%) Male: 195 (55%) **Race/ethnicity (n [%]):** Caucasian: 348 (99%)	**1) Blood pressure:** Results for ITT population (n = 237 candesartan, 116 lisinopril) Seated BP at 26 weeks: Candesartan/HCTZ: SBP 151.1± 19.1; DBP 93.0 ± 9.3 Lisinopril/HCTZ: SBP 145.9 ± 18.4; DBP 91.2 ± 8.4 Direct statistical testing NR; analyses of adjusted mean change results have p-values > 0.05. Response rates at 26 wk (seated DBP ≤ 90 mm Hg and/or reduction of ≥ 10 mm Hg from baseline): Candesartan/HCTZ: 129/237 (54.4%) Lisinopril/HCTZ: 72/116 (62.1%)	**General comments:** - Patients withdrawn if mean sitting BP > 180/100 at 2 visits 2-4 weeks apart, resulting in high level of withdrawal prior to 26-wk endpoint **Quality assessment:** Overall rating: Fair Comments: - Not clear if there was a run-in period (mentioned in results, but not methods) - Because no clear run-in, comparison is of patients' prior BP treatment and treatment with study drug; since prior treatment varied, significance of change observed is unclear; would have been better to have placebo run-in to get baseline BP or at least to group results by

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Blinding: - Patients: Yes (double-dummy) - Providers: Yes - Assessors of outcomes: Yes **Was allocation concealment adequate?:** Yes (although blocks of 3 were used, central randomization should have controlled for this) **Baseline/run-in period:** NR **Duration of treatment:** 26-30 wk; outcomes reported at 26 wk **Duration of post-treatment followup:** NA	**Baseline blood pressure:** Seated trough BP assessed using a fully automated device (Omron HEM-705CP). Mean of 3 measurements taken at 2-min intervals after patient seated for 5 min. Candesartan/ HCTZ / Lisinopril/ HCTZ SBP: 169.2 ± 17.2 / 163.3 ± 16.9 DBP: 102.9 ± 5.5 / 101.8 ± 4.9 **Concurrent medications (n [%]):** No other antihypertensives allowed **Comorbidities (n [%]):** NR (patients reported to be similar across groups in race, height, BMI, medical history, duration of hypertension, and WHO stage.) **Recruitment setting:** NR **Inclusion criteria:** - Age 20-80 yr - Primary HTN - Diastolic BP 95-115 on 2 occasions 1-2 wk apart, 24 hr after antihypertensive monotherapy **Exclusion criteria:** - Women of child-bearing potential	p = 0.094 Other outcomes reported: BP control rates (seated DBP ≤ 90 mm Hg) Mean seated BP at 2 and 12 wk (Figure 1) Standing BP outcomes Some outcomes also reported for per-protocol population **2) Rate of use of a single antihypertensive agent for BP control:** Study drugs both combination agents; no other antihypertensives medications allowed **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Candesartan / Lisinopril Pts with AEs 164 (68.9%) / 93 (79.5%) Atrributable AEs 80 (33.6%) / 54 (46.2%) Withdrawn d/t AE 14 (5.9%) / 14 (12.0%) 2 cases of angioedema were reported in the lisinopril group (2/116 = 1.7%) vs. none in the candesartan group **6) Specific adverse events:** Candesartan / Lisinopril Dizziness/vertigo 11.8% / 15.4%	prior drug type - Difficult to tell how many patients withdrew and the reasons for withdrawal - Very little baseline information about the patients **Applicability:** - Racially homogenous – all white northern European patients - Recruitment setting not described - Low dose of lisinopril used

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results		Comments/ quality/applicability
		- Recent significant CV event or condition - Concomitant drugs with BP modulating effects -Contraindications to any of study drugs -Severe concomitant disease -Conditions associated with poor compliance	Headache 11.8% Viral infection 8.8% Fatigue 5.9% Back pain 5.5% Resp infection 5.5% Pain 5.0% Cough 4.6% Myalgia 4.2% Nausea 4.2% Accident/injury NR Pharyngitis NR **7) Persistence/adherence:** As assessed by tablet count, 90% of patients took 90-110% of study medications – similar in two treatment groups **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	8.5% 7.7% 6.0 5.1% 9.4% NR 23.1% 6.0% NR 4.3% 4.3%	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr>
<td>Menne, Farsang, Deak, et al., 2008

#327</td>
<td>Geographical location: 24 primary and hospital centers in Hungary & Germany

Study dates: Aug 2004 – May 2007

Funding source: Novartis Pharma GmbH

Interventions:
- Valsartan 320 mg (n = 43)
- Lisinopril 40 mg (n = 47)
- Valsartan 320 mg/lisinopril 20 mg (n = 43)

Titration in 3 steps over 6 weeks:
Valsartan 80-320 mg
Lisinopril 10-40 mg
Valsartan/Lisinopril 80/10 – 320/20

Were additional anti-hypertension medications allowed: Yes

If Yes to above, was this done:
Per protocol

Study design:
RCT, parallel-group

Blinding:
- Patients: Yes
- Providers: Yes
- Assessors of outcomes: Yes

Was allocation concealment adequate?: Yes</td>
<td>Number of patients: N = 133
- Screened for inclusion: 331
- Eligible for inclusion: NR
- Randomized: 133
- Began treatment: 133
- Completed treatment: 115
- Withdrawals/losses to followup: 18 (129 were analyzed: 4 were not included in analyses b/c no measurements after 12 wks)

Age:
Mean (SD): 58.6 ±10.8

Sex (n [%]):
Female: 37 (28.7%)
Male: 92 (71.3%)

Race/ethnicity (n [%]): NR

Baseline blood pressure:
Mean (± SD):
<table>
<tr><td></td><td>SBP</td><td>DBP</td></tr>
<tr><td>Lisinopril</td><td>153.0 ± 14.3</td><td>90.6 ± 8.3</td></tr>
<tr><td>Valsartan</td><td>153.1 ± 16.0</td><td>91.9 ± 7.7</td></tr>
<tr><td>Combo</td><td>150.4 ± 13.7</td><td>90.1 ± 8.4</td></tr>
</table>
Concurrent non-hypertension medications (%):
<table>
<tr><td></td><td>L</td><td>V</td><td>V/L</td></tr>
<tr><td>HCTZ</td><td>19.1</td><td>23.3</td><td>11.6</td></tr>
<tr><td>Amlodipine</td><td>19.1</td><td>9.3</td><td>11.6</td></tr>
<tr><td>Both</td><td>29.8</td><td>27.9</td><td>30.2</td></tr>
</table>
HTN medication at baseline (%):</td>
<td>1) Blood pressure:

Reduction in seated trough BP – 12 weeks:
<table>
<tr><td></td><td>SBP</td><td>DBP</td></tr>
<tr><td>Lisinopril</td><td>14.1</td><td>10.0</td></tr>
<tr><td>Valsartan</td><td>16.0</td><td>11.8</td></tr>
<tr><td>Combo</td><td>16.9</td><td>11.5</td></tr>
</table>
Reduction in seated trough BP – 30 weeks:
<table>
<tr><td></td><td>SBP</td><td>DBP</td></tr>
<tr><td>Lisinopril</td><td>14.0</td><td>11.1</td></tr>
<tr><td>Valsartan</td><td>16.0</td><td>10.9</td></tr>
<tr><td>Combo</td><td>16.4</td><td>11.5</td></tr>
</table>
No statistical differences

% patients with normal BP at 30 weeks:
<table>
<tr><td></td><td>L</td><td>V</td><td>V/L</td></tr>
<tr><td>%</td><td>25.5</td><td>26.2</td><td>30.0</td></tr>
</table>
P = 0.034 for between-groups comparison

2) Rate of use of a single antihypertensive agent for BP control:
Lisinopril: 32%
Valsartan: 39.5%
Valsartan/lisinopril: 46.6%

3) Mortality: 1 death each in lisinopril and combination arms

4) Morbidity: NR

5) Safety:
<table>
<tr><td></td><td>All AE N (%)</td><td>AE with d/c</td><td>AE due to drug</td></tr>
<tr><td>Lisinopril</td><td>29 (61.7)</td><td>4 (8.5)</td><td>6 (12.8)</td></tr>
</table></td>
<td>General comments:
- Limited to patients with microalbuminuria
- Missing data were imputed by last observation carried forward, which can introduce bias

Quality assessment:
Overall rating: Good

Comments:
- Adequate randomization, blinding
- Patients comparable at baseline and treated similarly during study

Applicability:
- Non-US setting
- Limited to patients with HTN and microalbuminuria</td>
</tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Baseline/run-in period: No meds for 2 weeks, then single-blind placebo for 1 week

Duration of treatment: 30 weeks

Duration of post-treatment followup: NR

	L	V	V/L
ACEI	59.6	51.1	53.5
ARB	23.4	11.7	9.4
CCB	19.1	16.3	23.3
BB	38.1	27.9	32.5
Diuretic	19.3	16.3	11.7

Comorbidities (%):

	L	V	V/L
Cardiac d/o	25.5	11.6	18.6
Type 2 DM	74.5	74.4	76.7
Hyper-lipidemia	51.1	41.9	34.9

Recruitment setting: Primary and hospital centers in Hungary and Germany

Inclusion criteria:
- Age 18-75
- Essential HTN defied as mean sitting DBP 85-110 mmHg
- Microalbuminuria (women 3.5-35 mg/mmol, men 2.5-25 mg/mmol)

Exclusion criteria:
- Primary kidney disease
- Renal impairment (CrCL < 30 ml/min)
- Heart failure
- Significant arrythymia/bradycardia
- Relevant valvular disease
- Type 1 DM
- Uncontrolled Type 2 DM (Hgba1c > 8%)
- History of MI, PTCA, CABG, CVA in past 12 months
- Unstable angina

Valsartan	27 (62.8)	3 (7.0)	8 (18.6)
Combo	31 (72.1)	3 (7.0)	11 (25.6)

6) Specific adverse events:

	L	V	V/L
Hyper-kalemia	10.6 %	11.6 %	18.6 %
Cough	4.3%	0	2.3 %
Hypo-tension	4.3%	9.3%	11.6 %

(Hyperkalemia data taken from text, pg 1864, not Table 3)

7) Persistence/adherence: NR

8) Lipid levels: NR

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: NR

11) LV mass/function: NR

12) Creatinine/GFR: NR

13) Proteinuria:
UACR (mg/mmol)

	Baseline	30 weeks
Lisinopril	9.6	5.7
Valsartan	9.1	4.5
Combo	9.5	3.6

Difference between ACEI and ARB nonsignificant
Combo better than lisinopril (p = 0.029)

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Renal transplantation - Severe hepatic disease/failure - Malignancy or history of malignancy in past 5 yrs - Systemic inflammatory disease - Pregnant or breastfeeding - Psychiatric disease - Alcohol or drug abuse	% patients with resolution of microalbuminuria at 30 weeks L: 17; V: 31; V/L: 38 P = 0.034 for between-groups comparison	
Mimran, Ruilope, Kerwin, et al., 1998 **#1602**	**Geographical location:** Multicenter trial (France??, Spain ??) **Study dates:** NR **Funding source:** Bristol-Myers Squibb/Sanofi **Interventions:** - Irbesartan 75 mg (n = 98) - Enalapril 10 mg (n = 102) One capsule once a day between 6 and 10 a.m. If DBP at trough was ≥ 90 mm at weeks 4 or 8, dosage was doubled (irbesartan increased from 150 mg, enalapril to 20 mg). If SBP remained ≥ 90 mm at week 8 doses doubled again (300 mg and 40 mg). **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: Yes - Assessors of outcomes: NR	**Number of patients:** - Screened for inclusion: - Eligible for inclusion: - Randomized: 200 - Began treatment: 200 - Completed treatment: 191 - Withdrawals/losses to followup: 9, 4 due to AEs, 3 at patient request, 2 lost to followup **Age:** Mean (SD): 58.3 Median: NR Range: 145 < 65 yr; 55 ≥ 65 yr; 15 ≥ 75yr **Sex (n [%]):** Female: 99 Male: 101 **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Measured by a standard calibrated mercury sphygmomanometer. Mean of 3 readings take 1 min apart used. Seated and standing readings taken. Baseline seated BP:	**1) Blood pressure:** Numerical results not reported. Both groups: Statistically significant decreases from baseline trough SBP and DBP at all measured time points (weeks 2-12). No statistically significant difference between regimes with respect to decrease in SBP or DBP. Results consistent across both sexes and all age groups. Pts maintained on lowest doses: DBP decreased by 15 mm within 4 weeks with no further decreases. Patients whose dose was doubled once: Mean DBP decreased by 8 mm with lowest doses, but mean DBP was above 90 mm. Doubling was associated with additional decrease of 5 mm between wks 4 and 8 for both groups, resulting in a decrease from baseline of 13 mm with little change thereafter. Patients whose dose was doubled twice: DBP decreased by 5 mm and 1 mm in both groups, resulting in a total decrease from baseline of 11 mm and 8 mm in enalapril and irbesartan groups. At 12 wks: - Mean DBP was higher in those titrated than those maintained at lowest dosages.	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: No description of sites, or criteria for selection of sites **Applicability:** Race of patients not mentioned

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Was allocation concealment adequate?: NR

Baseline/run-in period: 4-to 5-wk single-blind placebo lead-in period

Duration of treatment: 12 weeks

Duration of post-treatment followup: NA

	Enalapril	Irbesartan
SBP:	164.9 ± 12.8	163.9 ± 12.5
DBP:	101.8 ± 4.2	101.0 ± 4.1

Concurrent medications (n [%]):
NR (though see Exclusion criteria)

Comorbidities (n [%]):
NR (though see Exclusion criteria)

Recruitment setting:
NR

Inclusion criteria:
- Lead-in medication consumption > 80% and < 120%
- DBP on days 22-29 (or days 29 and 36) between 95 mm Hg and 110 mm Hg inclusive, values on each day not differing by more than 8 mm Hg
- Age ≥ 18 yr

Exclusion criteria:
- Concomitant diseases or medications that would present a safety hazard or interfere with assessment of safety or efficacy of study medications
- Women who were pregnant, lactating, or of child-bearing potential

- 66% of irbesartan and 63% of enalapril group were normalized (DBP < 90mm).

2) Rate of use of a single antihypertensive agent for BP control (different doses): NR

3) Mortality: NR

4) Morbidity: NR

5) Safety:
(see next page)

	Enalapril (%) (n = 102)	Irbesartan (%) (n = 98)
Adverse drug experience	26	19
AE	43	45
Serious AE	1.0	4.1
Discontinued	2.9	1.0

6) Specific adverse events:
Patients with cough (%):
Enalapril: 15%
Irbesartan: 7%

7) Persistence/adherence: NR

8) Lipid levels: NR

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: NR

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td></td><td></td><td>11) LV mass/function: NR

12) Creatinine/GFR:
Mean change in lab parameters at week 12 (95% CI):

<table><tr><td></td><td>Enalapril n = 96</td><td>Irbesartan n = 94</td></tr><tr><td>Creatinine (mg/dL)</td><td>0.03 (0 to 0.06)</td><td>0.01 (-0.02 to 0.04)</td></tr></table>
13) Proteinuria: NR</td><td></td></tr>
<tr><td>Mogensen, Neldam, Tikkanen, et al., 2000

#1603</td><td>Geographical location: 37 sites in Australia, Denmark, Finland, and Israel

Study dates: NR

Funding source: AstraZeneca

Interventions:
Randomized to 1 of 4 groups by treatment in 2 x 12-week periods:
- Candesartan/candesartan (n = 66)
- Lisinopril/lisinopril (n = 64)
- Candesartan/candesartan + lisinopril (n = 34)
- Lisinopril/candesartan + lisinopril (n = 35)

Doses were: candesartan 16 mg, lisinopril 20 mg

Co-interventions:
Some patients also received HCTZ 12.5, but protocol for giving this not described</td><td>Number of patients:
- Screened for inclusion: NR
- Eligible for inclusion: NR
- Randomized: 199
- Began treatment: 198
- Completed treatment: NR
- Withdrawals/losses to followup: 2 excluded from 12- and 24-wk analyses (1 never took study med, 1 provided no efficacy data); additional 53 excluded from 24-wk analysis (“most because their DBP was below 80 mm Hg”)

Age:
Mean (SD): 59.8
Median: NR
Range: NR

Sex (n [%]):
Candesartan/lisinopril:
Female: 99 (50%)
Male: 98 (50%)

Race/ethnicity (n [%]): NR</td><td>1) Blood pressure:
Mean post-treatment BP values NR (except in Figure 2)

Mean reduction (95% CI) in seated trough BP at 12 wk:
<table><tr><td></td><td>Cande-sartan (n = 99)</td><td>Lisinopril (n = 98)</td><td>Adjusted* mean diff. between groups</td></tr><tr><td>SBP</td><td>12.4 (9.1 to 15.8)</td><td>15.7 (12.2 to 19.2)*</td><td>3.3 (-1.5 to 8.2) p = 0.18</td></tr><tr><td>DBP</td><td>9.5 (7.7 to 11.2)</td><td>9.7 (7.9 to 11.5)</td><td>0.02 (-2.3 to 2.7) p > 0.20</td></tr></table>*Adjusted for center, treatment, baseline value, weight, and change in DBP

Mean reduction (95% CI) in seated trough BP at 24 wk:
<table><tr><td></td><td>Candesartan (n = 49)</td><td>Lisinopril (n = 46)</td></tr><tr><td>SBP</td><td>14.1 (8.9 to 19.2)</td><td>16.7 (11.4 to 21.9)</td></tr><tr><td>DBP</td><td>10.4</td><td>10.7 (8.0 to</td></tr></table></td><td>General comments:
None

Quality assessment:
Overall rating: Fair

Comments:
- Primary results (mean post-treatment values) NR; report only differences from baseline
- 24-wk results not analyzed for candesartan vs. lisinopril, only the combination vs. each individual
- Addition of HCTZ permitted, but protocol for this not described

Applicability:
- All patients had type 2 diabetes and microalbuminuria
- Recruitment not described</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			(7.7 to 13.1) 13.5) No statistical tests reported for comparison between candesartan and lisinopril monotherapies at 24 wk	
	Study design: RCT, parallel-group (performed as a mixed study; analyzed as a parallel-group study) **Blinding:** - Patients: Yes (double-dummy) - Providers: Yes - Assessors of outcomes: Yes **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 4-wk placebo run-in **Duration of treatment:** 24 wk **Duration of post-treatment followup:** NA	**Baseline blood pressure:** Seated trough BP measured after 5-min rest using automatic device (Omron HEM-705 CP). Mean of 3 measures separated by 2 min analyzed. Candesartan (n = 99) / Lisinopril (n = 98) SBP 162.7 ± 17.7 / 162.6 ± 17.6 DBP 96.0 ± 6.2 / 95.7 ± 6.2 **Concurrent medications (n [%]):** Oral anti-diabetic drugs: "about 80%" of patients in both groups Insulin: 20% in both groups **Comorbidities (n [%]):** All patients with hypertension, diabetes type 2 and microalbuminuria **Recruitment setting:** Tertiary hospitals and primary care clinics **Inclusion criteria:** - Age 30-74 yr - Type 2 diabetes - Urinary albumin:creatinine ratio 2.5-25 mg/mmol, diastolic BP 90-110 mmHg after 2 and 4 wk of placebo, respectively **Exclusion criteria:** - BMI ≥ 40 kg/m^2 - SBP > 200 mm Hg	**2) Rate of use of a single antihypertensive agent for BP control:** Number of patients given HCTZ in addition to study drugs at 12 wk: Candesartan: 18/99 (18%) Lisinopril: 27/98 (28%) Number of patients given HCTZ in addition to study drugs at 24 wk: Candesartan: 7/49 (14%) Lisinopril: 6/46 (13%) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** 14/197 stopped treatment due to AEs: 5 due to dizziness, weakness, or both (candesartan 2, lisinopril 2, combination 1); 3 due to cough (all lisniopril). Others not specified. **6) Specific adverse events:** NR except AEs leading to withdrawal (see immediately above) **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:**	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td></td><td>- Non-diabetic cause of secondary hypertension
- Cardiovascular event < 6 mo
- Serum creatinine ≥ 130 x6d mol/L in women and ≥ 150 x 6d ml/L in men
- Serum potassium > 5.5 mmol/L
- HbA1c > 10%
- Pregnancy or potential pregnancy or breastfeeding</td><td>No clear changes in mean values for HbA1c from baseline to 12 or 24 wk in any of the treatment groups (no quantitative data reported)

11) LV mass/function: NR

12) Creatinine/GFR: NR

13) Proteinuria:
Mean post-treatment urinary albumin:creatinine ratios NR

Mean reduction in urinary albumin:creatinine ratio (%, with 95% CI) at 12 wk:
<table><tr><td>Candesartan (n = 99)</td><td>Lisinopril (n = 98)</td><td>Adjusted* mean diff. between treatments</td></tr><tr><td>30 (15 to 42)</td><td>46 (35 to 56)</td><td>30 (1 to 71)
p = 0.58</td></tr></table>*Adjusted for center, treatment, baseline value, weight, and change in DBP

Mean reduction in urinary albumin:creatinine ratio (%, with 95% CI) at 24 wk:
<table><tr><td>Candesartan (n = 49)</td><td>Lisinopril (n = 46)</td><td>Adjusted* mean diff. between treatments</td></tr><tr><td>24 (0 to 43)</td><td>39 (20 to 54)</td><td>Not reported</td></tr></table>*Adjusted for center, treatment, baseline value, weight, and change in DBP</td><td></td></tr>
<tr><td>Naidoo, Sareli,</td><td>Geographical location: 21 centers in South Africa, Hungary,</td><td>Number of patients:
- Screened for inclusion: NR</td><td>1) Blood pressure:
Mean BP at 12 wk (entire sample):</td><td>General comments:
- Patients with inadequate BP</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Marin, et al., 1999 **#1604**	Czech Republic, Slovak Republic, Argentina, Brazil, and Colombia **Study dates:** NR **Funding source:** Merck **Interventions:** - Losartan 100 mg + HCTZ 25 mg (n =176) - Enalapril 10 mg ± HCTZ 25 mg (n =173) Dose titration and co-interventions: Beginning at wk 2, amlodipine 5 mg could be added if DBP > 105, with titration to 10 mg if DBP > 90 at next visit Patients with inadequate BP control (SBP > 220 and/or DBP > 120 or increased > 15 from baseline) at 2 successive measurements at least 3 days apart were discontinued from the trial **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes **Was allocation concealment adequate?:** NR	- Eligible for inclusion: NR - Randomized: 349 - Began treatment: 325 - Completed treatment: 311 - Withdrawals/losses to followup: 38, some before and some after starting treatment (12 due to AEs, 12 due to protocol violations, 7 lost to followup, 5 lack of cooperation, 2 insufficient response) **Age:** Mean (SD): 53.25 Median: NR Range: NR **Sex (n [%]):** Female: 201 (58%) Male: 148 (42%) **Race/ethnicity (n [%]):** Caucasian: 174 (50%) Black: 98 (28%) Other: 77 (22%) **Baseline blood pressure:** Seated trough BP measured 3 times after a 5-min rest using a standard mercury sphygmomanometer; average of 3 readings used	Losartan/HCTZ (n = 173) / Enalapril/HCTZ (n = 173) SBP 139.7 ± 17.6 / 140.5 ± 15 DBP 88.7 ± 10.1 / 88.4 ± 8.3 Mean BP for patients *not* receiving adjunctive amlodipine: Losartan/HCTZ (n = 129) / Enalapril/HCTZ (n = 124) SBP baseline 159.8 ± 13.7 / 161.5 ± 15.1 SBP 12 wk 137.3 ± 16.6 / 139.2 ± 14.6 DBP baseline 103.0 ± 5.8 / 103.2 ± 7.0 DBP 12 wk 87.1 ± 10 / 87.5 ± 8.7 Note: Ns reported above are as given in the relevant data tables; varying figures given in text and other tables Authors reported that "both regimens were effective in black (n = 54 losartan/HCTZ; n = 44 enalapril/HCTZ) and non-black patients (data not shown)" BP control rates (control not clearly defined): Losartan/HCTZ: 63% Enalapril/HCTZ: 58.4% **2) Rate of use of a single antihypertensive agent for BP control:** NA; all patients taking a combination agent ± additional therapy **3) Mortality:** NR **4) Morbidity:** NR	control (SBP > 220 and/or DBP > 120 or increased > 15 from baseline) at 2 successive measurements at least 3 days apart were discontinued from the trial **Quality assessment:** Overall rating: Fair Comments: - Varying numbers of patients reported in text and tables - 12-wk outcomes compared with prestudy treatment in primary statistical analysis **Applicability:** - Recruitment setting not described - Extensive exclusion criteria

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Baseline/run-in period: 2 days no meds **Duration of treatment:** 12 wk **Duration of post-treatment followup:** NA	**Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** - Moderate or severe hypertension (DBP > 105) - Inadequate control on 2 or more agents (DBP > 90) - At least on drug-related symptom that might be alleviated by medication switch **Exclusion criteria:** - On ACEI prior to study start - Serious AE on ACEI, diuretic, or ARB - Malignant or secondary hypertension - SBP > 220 - Significant CV, GI, hepatic, or blood/coagulation disorders - Unstable diabetes - Obesity (arm girth > 41 cm) - Potassium < 3.5 or > 5.5 mEq/L - Serum creatinine > 150 umol/L - Bun > 12.5 mmol/L - Alanine or aspartate amino-transferase value > 50% upper limit normal - Proteinuria or hematuria - Cancer - AIDS - Absence of a kidney - Alcohol or drug abuse - Need for treatment with beta-	**5) Safety:** No. of patients with ≥ 2 drug-related AEs: Losartan/HCTZ: 29 (16.5%) Enalapril/HCTZ: 37 (21.4%) Withdrawals due to AEs: Losartan/HCTZ: 5 (2.8%) Enalapril/HCTZ: 7 (4.0%) Withdrawals due to drug-related AEs: Losartan/HCTZ: 3 (1.7%) Enalapril/HCTZ: 3 (1.7%) No serious AEs judged to be drug-related **6) Specific adverse events:** AEs not necessarily drug-related: | | Losartan/ HCTZ (n = 173), % | Enalapril/ HCTZ (n = 170), % | |---|---|---| | Headache | 19.1 | 20.6 | | Palpitations | 15.6 | 13.5 | | Tired | 14.5 | 17.1 | | Dizzy | 11.0 | 5.3 | | Nervous | 12.1 | 9.4 | | Flushing | 10.4 | 6.5 | | Weakness | 9.2 | 7.1 | | Swollen ankles | 5.8 | 5.3 | | Muscle pain | 6.4 | 8.8 | | Cough | 6.9 | 16.5* | | Cold hands/feet | 6.4 | 7.6 | * p = 0.005, enalapril/HCTZ vs. losartan/HCTZ **7) Persistence/adherence:** NR **8) Lipid levels:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td></td><td>blockers, psychotropics, antidepressants, cimetidine, oral contraceptives, steroids, corticotropin, or lithium</td><td>9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: NR

11) LV mass/function: NR

12) Creatinine/GFR: NR

13) Proteinuria: NR</td><td></td></tr>
<tr><td>Nakamura, Kawachi, Saito, et al., 2009

#19</td><td>Geographical location: Gunma, Japan

Study dates: NR

Funding source: Ministry of Education, Culture, Sports, Science and Technology of Japan

Interventions:
Perindopril 2-8 mg (n = 27)
Telmisartan 20-80 mg (n = 26)

Mean doses at study end:
4.2 ± 0.4 mg/day
44.6 ± 2.3 mg/day

Were additional anti-hypertension medications allowed: Yes

If Yes to above, was this done:
At discretion of clinician/investigator
(allowed to keep existing anti-HTN)</td><td>Number of patients: N = 53
- Screened for inclusion: NR
- Eligible for inclusion: NR
- Randomized: 53
- Began treatment: 53
- Completed treatment: 51
- Withdrawals/losses to followup: 2

Age:
Mean (SD): 64.8 ±2.5
Range: 33 - 84

Sex (n [%]):
Female: 30 (56.6%)
Male: 23 (43.4%)

Race/ethnicity (n [%]): NR
(assume 100% Japanese)

Baseline blood pressure:
Figure only, appears to be 158/88 for both groups

Concurrent non-hypertension medications (n [%]):<table><tr><td></td><td>Perind</td><td>Telmis</td></tr><tr><td>CCB</td><td>13 (48%)</td><td>14 (54%)</td></tr></table></td><td>1) Blood pressure:
BP at 48 weeks, mean (SD)<table><tr><td></td><td>SBP</td><td>DBP</td></tr><tr><td>Perindopril</td><td>137.2 (1.9)</td><td>77.0 (1.9)</td></tr><tr><td>Telmisartan</td><td>136.8 (2.6)</td><td>76.8 (2.3)</td></tr></table>Between-groups comparison not statistically significant

2) Rate of use of a single antihypertensive agent for BP control: NR

3) Mortality: NR

4) Morbidity: NR

5) Safety: NR

6) Specific adverse events:
Cough: 2 perindopril group (causing study discontinuation; were not included in analyses)

7) Persistence/adherence: NR

8) Lipid levels:
LDL (mg/dL)<table><tr><td></td><td>Perindopril</td><td>Telmisartan</td></tr></table></td><td>General comments:
None

Quality assessment:
Overall rating: Fair

Comments:
- No description of blinding, randomization method
- Small sample size (powered for change in aldosterone)
- No description of dose escalation
- Low attrition; all participants accounted for at study end

Applicability:
- Non-US setting</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Study design:
RCT, parallel-group

Blinding:
- Patients: NR
- Providers: NR
- Assessors of outcomes: NR

Was allocation concealment adequate?: NR

Baseline/run-in period: None

Duration of treatment: 48 weeks

Duration of post-treatment followup: NR

Diuretic	5 (19%)	4 (15%)
α blocker	4 (15%)	2 (8%)
BB	6 (22%)	8 (31%)

Comorbidities (n [%]):

	Perind	Telmis
DM	5 (19%)	3 (12%)
Lipids	8 (30%)	11 (42%)
CVD	3 (11%)	1 (4%)
CVA	0	2 (8%)
Smoking	3 (11%)	4 (15%)
ETOH	11 (41%)	8 (31□)

Recruitment setting: NR

Inclusion criteria:
-Essential HTN (SBP > 140 or DBP > 90)

Exclusion criteria:
- Secondary HTN
- ACEI or ARB in past 6 months

Baseline	119 ± 7	116 ± 5
24 weeks	122 ± 6	117 ± 5
48 weeks	122 ± 6	112 ± 8

HDL (mg/dL)

	Perindopril	Telmisartan
Baseline	51.7 ± 2.5	52.5 ± 4.6
24 weeks	52.1 ± 2.1	51.1 ± 4.3
48 weeks	54.1 ± 2.5	50.6 ±4.1

Triglyceride (mg/dL)

	Perindopril	Telmisartan
Baseline	152.7 ± 17.7	163.0 ± 20.6
24 weeks	141.1 ± 11.4	174.6 ± 22.9
48 weeks	133.8 ± 11.8	153.5 ± 18.2

Within-group changes from baseline and between-groups comparisons were not statistically significant

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control:
Plasma glucose (mg/dL)

	Perindopril	Telmisartan
Baseline	110 ± 6	113 ± 4
24 weeks	118 ± 7	113 ± 7
48 weeks	104 ± 4	112 ± 7

HbA1c (%)

	Perindopril	Telmisartan
Baseline	5.5 ± 0.2	5.6 ± 0.3
24 weeks	5.5 ± 0.1	5.6 ± 0.3
48 weeks	5.6 ± 0.2	5.7 ± 0.3

Between-groups comparison not statistically significant

11) LV mass/function: NR

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			12) Creatinine/GFR: Serum creatinine Perindopril: Baseline 0.77 ± 0.03; 24 weeks 0.79 ± 0.04; 48 weeks 0.80 ± 0.04 Telmisartan: Baseline 0.73 ± 0.05; 24 weeks 0.79 ± 0.07; 48 weeks 0.75 ± 0.06 **13) Proteinuria:** Urine albumin/creatinine ratio Perindopril: Baseline 23.8 ± 8.3; 24 weeks 40.8 ± 23.2; 48 weeks 41.5 ± 21.8 Telmisartan: Baseline 58.2 ± 34.1; 24 weeks 55.5 ± 34.2; 48 weeks 47.9 ± 28.5 Between-groups comparison not statistically significant	
Neutel, Frishman, Oparil, et al., 1999 **#1605**	**Geographical location:** 44 centers across US **Study dates:** NR **Funding source:** NR **Interventions:** - Telmisartan 40-160 mg qd (n = 385) - Lisinopril 10-40 mg qd (n = 193) Dosage titration and co-interventions: At wk 4, patients with uncontrolled DBP (≥ 90 mm Hg) were titrated to dose level 2 (telmisartan 80 mg, lisinopril 20 mg); if DBP still uncontrolled at wk 8, then titrated to dose level 3 (telmisartan 160 mg, lisinopril 40 mg). If DBP still uncontrolled at wk 12, but DBP reduced by ≥ 10 mm Hg from baseline, then	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 578 - Began treatment: 578 - Completed treatment: 448? - Withdrawals/losses to followup: 136 during dose-titration period (125 treatment failures, 11 no post-randomization BP data); 25 during maintenance phase (protocol deviations or invalid data) **Age:** Mean (SD): 53.5 Median: NR Range: NR **Sex (n [%]):** Female: 195 (34%) Male: 383 (66%) **Race/ethnicity (n [%]):**	**1) Blood pressure:** Mean change in BP at 48 wk (in mm Hg; all analyzable completers, n's uncertain): Telmisartan / Lisinopril SBP: -21.1 / -19.3 DBP: -16.3 / -15.4 p = NS Mean change in BP at 48 wk among patients who completed on monotherapy (in mm Hg; n's uncertain): Telmisartan / Lisinopril SBP: -17.7 / -18.6 DBP: -15.9 / -15.5 **2) Rate of use of a single antihypertensive agent for BP control:** Telmisartan: 44% Lisinopril: 48%	**General comments:** - Study excluded large number of patients post-randomization who failed to respond to treatment (DBP ≥ 90) **Quality assessment:** Overall rating: Fair Comments: - Randomization not described - Large number of non-responders excluded post-randomization - N's unclear for many outcomes **Applicability:** - Recruitment not described - Non-responders excluded during study - Supine BP used

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	HCTZ 12.5 mg added; remaining uncontrolled patients dropped from study. For patients on HCTZ, this could be titrated up to 25 mg if BP control lost during maintenance phase. If DBP ≥ 90 mm Hg on 2 consecutive study visit while patient taking max dose of HCTZ, then patient dropped from study **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: Yes - Assessors of outcomes: No **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 2- to 14-day withdrawal of previous antihypertensive med; 4-wk placebo run-in **Duration of treatment:** 48 wk after dose titration achieved **Duration of post-treatment followup:** NA	White: 433 (75%) Black: 102 (18%) Hispanic: 35 (6% Other: 8 (1%) **Baseline blood pressure:** Supine BP measured 3 times at 2-min intervals after patient rested in supine position for 5 min using mercury sphygmomanometer; average of 3 readings used Telmisartan / Lisinopril SBP 153.4 / 152.5 DBP 100.8 / 100.5 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR- 44 centers **Inclusion criteria:** - Mean supine DBP 95-114 on placebo (run-in period) **Exclusion criteria:** - Secondary hypertension - Patients excluded at various points during study if DBP ≥ 90	**3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Drug-related AEs: Telmisartan: 28% Lisinopril: 40% p = 0.001 Discontinuations due to cough: Telmisartan: 0.3% Lisinopril: 3.1% p = 0.007 Discontinuations due to angioedema: Telmisartan: 0 Lisinopril: 2 patients **6) Specific adverse events:** AEs considered to be drug-related: Telmisartan (n = 385), % / Lisinopril (n = 193), % Impotence 3 / 2 Headache 5 / 6 Fatigue 4 / 7 Cough 3 / 7* Dizzy 7 / 8 Dyspepsia 0 / 2 *p = 0.18 vs. telmisartan **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			11) LV mass/function: NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Onal, Altun, Onal, et al., 2009 **#27**	**Geographical location:** Ankara, Turkey **Study dates:** NR **Funding source:** LUT 04/61, Turkish Hypertension and Kidney Disease Foundation, Astra Zeneca **Interventions:** - Candesartan 8-16 mg/day (n = 17) - Lisinopril 10-20 mg/day (n = 16) - Age- and sex-matched controls (normotensive n = 16) **Were additional anti-hypertension medications allowed:** No **Study design:** RCT, parallel-group **Blinding:** - Patients: NR - Providers: NR - Assessors of outcomes: NR **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 1 week	**Number of patients:** N = 49 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 33 - Began treatment: 33 - Completed treatment: 33 - Withdrawals/losses to followup: 0 **Age:** Mean (SD): Hypertensive: 47 ±8 Normotensive: 42 ±10 **Sex (n [%]):** Hypertensive: Female: 22 (66.6%) Male: 11 (33.3%) All: Female: 31 (63.3%) Male: 18 (36.7%) **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Mean (SD) |	SBP	DBP
---	---	---
Candesartan	127 (6)	81 (6)
Lisinopril	131 (11)	84 (7)		**1) Blood pressure:** Mean (SD) |	SBP	DBP
---	---	---
Candesartan	117 (6)	72 (5)
Lisinopril	120 (9)	77 (6)	 There were no statistically significant differences between the medications. **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR	**General comments:** - Recruitment, randomization, and blinding were not described - Baseline demographics not described for 2 intervention arms - Small study and short duration - BP measures not described well - Randomized; all patients had complete data **Quality assessment:** Overall rating: Fair Comments: See general comments **Applicability:** - Recruitment/screening not described - Unable to assess baseline confounders between groups - Small study with no differences between groups noted (Type 2 error possible)

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	washout at start of trial if on any BP medication **Duration of treatment:** 3 months **Duration of post-treatment followup:** NA	**Concurrent non-hypertension medications (n [%]):** None **Comorbidities (n [%]):** NR **Recruitment setting:** Nephrology and general medicine outpatient clinics at Hacettepe University Hospital **Inclusion criteria:** Stage 1 HTN diagnosed after 24 h ambulatory blood pressure monitoring (ABPM), and was defined as having systolic and diastolic BPs over 140/90 mm Hg during the day or 120/80 mm Hg at night. For patients on BP medication, measurement occurred after stopping treatment for 1 week. **Exclusion criteria:** - Renal insufficiency of stage 2 and above - Hypertension of stage 2 and above - Diabetes - Signs or symptoms of cardiovascular, neoplastic or connective tissue disease, and of any evidence of organ fibrosis - Required use of antihypertensive drugs other than ACEI or ARB	**12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Ozturk, Sar, Bengi-Bozkurt, et	**Geographical location:** NR (authors from Turkey)	**Number of patients:** - Screened for inclusion: 289 charts reviewed retrospectively	**1) Blood pressure:** "The course of mean SBP and DBP throughout the study was similar (147.9 ±	**General comments:** None **Quality assessment:**

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
al., 2009 **#1667**	**Study dates:** NR **Funding source:** NR **Interventions:** 1) ACEI prescribed (N = 59) 2) ARB prescribed (N = 41) **Were additional anti-hypertension medications allowed:** Yes **If Yes to above, was this done:** At discretion of clinician/investigator "19 of the ACEI group (32%) and 15 of the ARB group (36%) were taking non-dihydopyridine class calcium channel blockers, and 29 of the ACEI group (49%) and 22 of the ARB group (53%) were taking other antihypertensive drugs" **Study design:** Retrospective chart review **Blinding:** - Patients: NA - Providers: NA - Assessors of outcomes: No **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Washout period(s):** NA	- Eligible for inclusion: 100 - Randomized: NA - Began treatment: 100 - Completed treatment: 100 - Withdrawals/losses to followup: 15 (11/59 = 19% in the ACEI group, and 4/41 = 10% in the ARB group) **Age:** Mean (SD): 61.8 (9.16) Median: NR Range: NR **Sex (n [%]):** Female: 45 (45%) Male: 55 (55%) **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** SBP, mean (SD): ACEI: 150 (27) ARB: 152 (22) P = 0.650 DBP, mean (SD): ACEI: 85 (10) ARB: 87 (13) P = 0.388 **Concurrent non-hypertension medications (n [%]):** 42 patients of the ACEI group (71%) and 35 of the ARB group (85%) were taking statins **Comorbidities (n [%]):** See inclusion criteria below. Mean duration of awareness of	16.5/83.3 ± 12.9 mm Hg in the ACEI group and 147.5 ± 16.0/83.7 ± 7.5 mm Hg in the ARB group; p = NS). At the last check, mean BP…was 135.8 ± 14.6/80.8 ± 10.1 mm Hg in the ACEI group, 140.0 ± 22.5/80.0 ± 5.3 mm Hg in the ARB group)." **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** ACEI: 2/59 (3.4%) ARB: 2/41 (4.9%) **4) Morbidity:** Incidence of dialysis during study period: ACEI: 7/59 (12%) ARB: 3/41 (7%) P = 0.20 **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Reasons for losses to followup or withdrawal not reported. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NA (all patients had DM) **10) Markers of carbohydrate metabolism/diabetes control:** Baseline HbA1c, g/dL (SD): ACEI: 8.31 (1.84) ARB: 7.58 (1.62) P = 0.118	Overall rating: Poor Comments: - Retrospective chart review (although it is possible that patients were followed prospectively—the reporting is ambiguous) - Inadequate reporting of methods and results - Possibility of significant selection bias **Applicability:** - Study conducted in Turkey (by inference) - Individual drugs not reported; results reported only as ACEI vs. ARB drugs

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Duration of treatment: Mean duration of followup 24.6 months (SD = 14.1) **Duration of post-treatment followup:** NA	DM = 15.7 years. **Recruitment setting:** Outpatient nephrology clinic **Inclusion criteria:** - Diabetic nephropathy, defined as type II diabetes, creatinine clearance <90 ml/min, and diabetic retinopathy - SBP ≥ 140 and/or DBP ≥ 90 mm Hg, or had been using anti-HTN drug(s) for HTN - Followed for at least 16 months and evaluated at least twice in the outpatient clinic prior to study entry **Exclusion criteria:** - Followed for < 6 months prior to study entry - Using an ACEI and ARB concurrently - Could not use an ACE or ARB for > 4 weeks - SBP < 140 mm and DBP < 90 at presentation - Any renal disease other than diabetic nephropathy (DNP) or any disease that might affect renal function independent of DNP - Non-diabetes-related renal or systemic comorbidities - Prior use of aldosterone blockers. - History of switching from ACEI to ARB or vice-versa Prior use of an ACE or ARB was	Followup HbA1c, g/dL (SD): ACEI: 7.9 (1.4) ARB: 7.73 (1.2) P = NS **11) LV mass/function:** NR **12) Creatinine/GFR:** Baseline creatinine, mg/dl (SD): ACEI: 1.75 (0.65) ARB: 1.66 (0.49) P = 0.441 Followup creatinine, mg/dl (SD): ACEI: 1.89 (0.86) ARB: 1.77 (0.62) P = NS Baseline estimated creatinine clearance, ml/min (SD): ACEI: 48.7 (17.5) ARB: 53.2 (16.7) P = 0.203 Followup estimated creatinine clearance, ml/min (SD): ACEI: 48.1 (18.1) ARB: 52.8 (17.6) P = NS **13) Proteinuria:** Baseline proteinuria, mg/day (SD): ACEI: 657 (1,871) ARB: 712 (3,184) P = 0.563 Followup proteinuria, mg/day (SD): ACEI: 307 (2,362) ARB: 466 (2,126)	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		not an exclusion criterion	P = NS "Although proteinuria decreased by 77% in the ACEI group and by 27% in the ARB group at 48 months (only 5 patients in the ACEI group and 6 patients in the ARB group could be followed until the 48th month, after the exclusion of those on dialysis or dead patients) in the statistical analysis, mean daily proteinuria did not show significant differences between both groups throughout the study."	
Patel, Remigio-Baker, Mehta, et al., 2007 **#173**	**Geographical location:** Records examined from across US **Study dates:** Jan 1, 2001 – Dec 31, 2003 **Funding source:** Novartis Pharmaceuticals Corporation **Interventions:** ARB: 10,245 (4.2%) ACEI: 78,616 (32.4%) CCB: 36,246 (14.9%) BB: 82,841 (34.1%) Diuretic: 34,934 (14.4%) **Were additional anti-hypertension medications allowed:** Yes **If Yes to above, was this done:** At discretion of clinician **Study design:** Other – retrospective longitudinal cohort study	**Number of patients:** N = 242,882 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NR - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR **Age:** Mean (SD): 54.9 ±15.7 **Sex (n [%]):** Female: 138,071 (56.8%) Male: 104,811 (43.2%) **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** NR **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** 78% of the study population had at least 1 comorbid condition with	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** 51.9% of ARB patients were persistent with their index therapy at 12 months, compared with 48.0% of ACEI patients, 40.3% of BB patients, 38.3% of CCB patients, and 29.9% of diuretic patients (no p value for comparison) After adjustment for covariates and compared with diuretic users, patients receiving an ARB were 52% more likely to be persistent, patients receiving an ACEI were 43% more likely to be persistent (no p	**General comments:** - Good design and dataset for research question - Adequate followup - Patient sample well defined and fairly similar among groups - Objective outcome criteria - Propensity scores used to match patients among BP drug class cohorts - Appropriate statistical analysis EXCEPT… - unable to confirm diagnosis of HTN (no clinic data) - Mostly descriptive data were reported without statistical testing. Results section uses terms "more" and "similar" but statistical testing was reported only twice, and it was for comparison of ACEI and ARB vs. others or each BP drug class vs. diuretics **Quality assessment:** Overall rating: Fair (Good if statistical testing was reported to back up comparison comments)

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Blinding: NA **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** 1 year **Duration of post-treatment followup:** NA	hypertension **Recruitment setting:** - Data drawn from the administrative pharmacy claims database from MedImpact, a large national pharmacy benefits manager that administers prescription benefit coverage to approximately 27 million persons across the United States - Database comprised employer corporations; unions; managed care organizations; health plans; insurance carriers; third-party administrators; and local, state, and federal employee programs **Inclusion criteria:** - Patients previously naïve to antihypertensive therapy - Started therapy with an ACEI, ARB, calcium channel blocker (CCB), b-blocker (BB), or diuretic - Age > 18 years - Filled at least 1 prescription for a target medication during the 3-year study identification period of Jan 1, 2001, through Dec 31, 2003 - Continuously benefit-eligible for at least 6 months preceding and 12 months following the index date **Exclusion criteria:** Claims for any target antihypertensive medications during the 6 months before their index date	value for comparison) The mean medication possession ratio (MPR) was similar for ACEI (59.2) and ARB (58.9) patients (no p value for comparison) Adjusted for covariates, the MPRs for patients receiving ARBs and ACEIs were not significantly different (no p value for comparison) but were higher than other drug classes ($p < 0.0001$) The percentage of patients classified as adherent (MPR > 80%) was similar for patients receiving ACEIs (39.2%) and ARBs (38.5%) (no p value for comparison) ARB patients had the longest time to therapy discontinuation (mean = 236.9 days), compared with patients utilizing other drug classes (no p value for comparison) Compared with patients who started diuretic therapy, patients who began antihypertensive monotherapy with ARBs (HR, 0.59; $P < 0.0001$), ACEIs (HR, 0.64; $P < 0.0001$), CCBs (HR, 0.86; $P < 0.0001$), or BBs (HR, 0.82; $P < 0.0001$) were all significantly less likely to discontinue their index therapy Most patients who discontinued index therapy did so within the first 30 days of starting therapy **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR	Comments: None **Applicability:** - Unable to verify comparison comments made in text because statistical testing not reported -Because study uses administrative data, unable to determine for certain whether discontinuation of therapy was due to AEs or other factors

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			10) Markers of carbohydrate metabolism/diabetes control: NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Rabbia, Silke, Carra, et al., 2004 **#1607**	Geographical location: NR; investigators from Italy and Ireland Study dates: NR Funding source: No external funding Interventions: - Fosinopril 10-20 mg (n = 19) - Irbesartan 150-300 mg (n = 19) - Atenolol 50-100 mg (n = 20) All once daily at 8 am Doses doubled if office BP was ≥ 140/90 mm No sodium or liquid intake restriction Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: No Was allocation concealment adequate?: NR Baseline/run-in period: 2-wk placebo-run-in period Duration of treatment: 14 weeks Duration of post-treatment followup: NA	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 58 - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR Age: Mean (SD): 38 ± 10 yr Median: NR Range: NR **Sex (n [%]):** Female: 27 Male: 31 Race/ethnicity (n [%]): NR **Baseline blood pressure:** Office BP measured 3 times by same physician in sitting position after 10 min of rest using a mercury sphygmomanometer, disappearance of phase V Korotkoff sound = diastolic pressure Baseline values: Fosinopril / Irbesartan SBP: 152 ± 11 / 151 ± 11 DBP: 97 ± 7 / 97 ± 6 ABPM obtained for 24 hr (results also reported)	**1) Blood pressure:** Office BP at 14 wk ($p < 0.001$ for all comparisons with baseline): Fosinopril / Irbesartan SBP: 129 ± 7 / 133 ± 9 DBP: 85 ± 4 / 87 ± 8 **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** Nr **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	**General comments:** - No racial distribution - Setting of study; no description (country? system? center selection? study clinicians?) - No data regarding numbers of patients screened, eligible for inclusion, or lost to followup Quality assessment: Overall rating: Fair Comments: - Setting of trial not described - Single-blind **Applicability:** - Race of patients not mentioned

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Concurrent medications (n [%]): None allowed during study **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: - Never treated mild hypertension with no evidence of target organ damage - SBP and DBP were ≥ 140 and ≥ 90 mm, respectively, on 3 consecutive days (3 measurements /day separated by 10-mm interval) after 15 min sitting position Exclusion criteria: - Clinical, biochemical, ECG or radiological evidence of end-organ damage or reported history of coronary artery disease - History of heavy alcohol consumption - Sec. hypertension def. as ABPM < 130/80 with persistently elevated office BP) and poor sleep quality during ABPM - No medications allowed during study		
Ragot, Ezzaher, Meunier, et al., 2002 **#1608**	Geographical location: 105 outpatient French Centers Study dates: NR Funding source: NR	Number of patients: - Screened for inclusion: 671 - Eligible for inclusion: 441 - Randomized: 441 - Began treatment: 441 - Completed treatment: NR - Withdrawals/losses to followup:	**1) Blood pressure:** Mean trough office BP at 12 wk (taken from Fig 3; SDs not reported): Telmisartan (n = 217) / Perindopril (n = 218) / P-value SBP	**General comments:** - Focus of article was comparison of self-measurement of BP and office measurement Quality assessment: Overall rating: Poor

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Interventions: - Telmisartan 40-80 mg (n =220) - Perindopril 4-8 mg (n = 221) Doses doubled at 6 wk if necessary Study design: RCT, parallel-group Blinding: - Patients: NR - Providers: NR - Assessors of outcomes: No – patients self measure BP Was allocation concealment adequate?: Yes - IVRS Baseline/run-in period: 3-wk run-in placebo period sitting DBP ≥ 90 and ≤ 110 and SBP < 180 Duration of treatment: 12 wk Duration of post-treatment followup: NR	73, 5 no BP measurements on treatment, 1 did not receive study med, 54 due to poor quality self BP measurement, 13 due to unspecified protocol violations - Per protocol population = 368 Age: Mean (SD): 55.3 ± 11.8 Median: NR Range: NR **Sex (n [%]):** Female: 197/435 (45%) Male: 238/435 (ITT pop) (55%) Race/ethnicity (n [%]): 421/435 = 97.5% white **Baseline blood pressure:** Trough office BP assessed using semiautomatic device (OMRON 705 CP); 3 measurements taken at 1-min intervals with patient sitting and after 5 min rest; mean analyzed Telmisartan (n = 217) / Perindopril (n = 218) SBP 158 ± 13 / 159 ± 13 DBP 98 ± 6 / 98 ± 6 **Concurrent medications (n [%]):** Anti-HTN therapy prior to study entry: 236 (54%) **Comorbidities (n [%]):**	144.0 148.0 p < 0.05 DBP 88.7 91.3 p < 0.005 Mean decrease in trough office DBP from baseline to 12 wk: Telmisartan: - 8.8 mm Hg Perindopril: -6.3 mm Hg p = 0.002 Adjusted mean difference (telmisartan vs. perindopril) for reduction in trough office SBP was -3.4 mm Hg (p = 0.016). Mean decreases NR. Normalized SBP at 12 wk (SBP < 140 mm Hg): Telmisartan: 97/217 (45%) Perindopril: 67/218 (31%) p < 0.005 Normalized DBP at 12 wk (DBP < 90 mm Hg): Telmisartan: 122/217 (56%) Perindopril: 96/218 (44%) p < 0.01 Results for self-BP measurement also reported **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR	Comments: - Not blinded - Large number of patients (n = 59) excluded from per-protocol analysis due to poor quality self-measurement of BP **Applicability:** - Results are more applicable than most of HTN trials review in that co-morbidities are presented in baseline table

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results		Comments/ quality/applicability
		Obesity 111 (25.5%) History of CV events 58 (13.5%) Type II DM 27 (6.5%) **Recruitment setting:** Outpatient French clinics Inclusion criteria: - Age ≥ 18 yr - Mild-moderate hypertension - Inadequate BP control or treatment side effect - 3-wk run-in placebo period sitting DBP ≥ 90 and ≤ 110 and SBP < 180 Exclusion criteria: - Patients with self BP measurement of poor quality during run-in period, poor compliance with treatment during run-in period - History of non response to ACEI or ARB - Suspicion of secondary HTN - Biliary disease - Non-postmenopausal women not using reliable contraception	**5) Safety:** Any AE: Telmisartan: 74 (34%) Perindopril: 70 (32%) **6) Specific adverse events:** Cough: Telmisartan: 2 (< 1%) Perindopril: 12 (5%) p = 0.007 **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR		
Rajzer, Klocek, and Kawecka-Jaszcz, 2003 **#1609**	Geographical location: Krakow, Poland Study dates: NR Funding source: University grant Interventions: - Quinapril 20 mg qd (n = 38 BP responders) - Losartan 100 mg (50 mg bid) (n	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 118 (for the larger study) - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR Age (n = 118 larger trial):	**1) Blood pressure:** Mean BP at 3 mo: Quinapril (n = 38) SBP 141 ± 23.7 DBP 92 ± 8.7 Mean BP at 6 mo: Quinapril	Losartan (n = 24) 132 ± 15.8 83 ± 9.2 Losartan	**General comments:** - Subgroup analysis of patients from a larger trial who responded to monotherapy at 3 mo (99/118) - Focus of article is effect of treatment on pulse wave velocity and plasma collagen markers Quality assessment: Overall rating: Poor

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	= 24 BP responders) - Amlodipine 10 mg qd (n = 37 BP responders) Dose titration and co-interventions: None, as subjects represent subgroup from larger trial who responded (BP ≤ 140/90 mm Hg) to monotherapy at 3 mo Study design: RCT, parallel-group Blinding: - Patients: No - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: NR Baseline/run-in period: 2-wk antihypertensive-free run-in period Duration of treatment: 6 mo Duration of post-treatment followup: NR	Mean (SD): 53.7 ± 9.06 Median: NR Range: NR **Sex (n [%]; n = 118 larger trial)*:** Female: 64 (54%) Male: 54 (46%) Race/ethnicity (n [%]): NR, but presumably 100% white **Baseline blood pressure:** Mean of 3 sphygmomanometer measurements "in standard conditions" Mean baseline values: Quinapril (n = 38) / Losartan (n = 24) SBP: 154 ± 22.5 / 155 ± 18.6 DBP: 97 ± 14.1 / 91 ± 13.5 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: - Mild to moderate hypertension according to WHO/ISH guidelines - BP adequately controlled (BP ≤ 140/90 mm Hg at 3 mo) on study	(n = 38) / (n = 24) SBP: 113 ± 14.6 / 125 ± 16.8 DBP: 86 ± 7.1 / 84 ± 8.1 No significant differences between groups for decrease from baseline at either timepoint (p-values NR) 24-hr ABPM values also reported **2) Rate of use of a single antihypertensive agent for BP control:** NA (response to monotherapy was the criterion for inclusion in this subgroup report) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** Measured but NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** LVMI was comparable across groups at baseline (116.9 ± 23.9 g/m^2) and did not change at 6 mo for any of the groups (data not shown)	Comments: - No information on recruitment setting, exclusion criteria, or comorbidities - No data on safety/AEs - Inclusion of only responders to monotherapy biases the results toward the null hypothesis of no difference in BP response, especially since there were fewer responders in the losartan group **Applicability:** - Subgroup of patients who responded to monotherapy - No information on recruitment setting, exclusion criteria, or comorbidities

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		drug monotherapy Exclusion criteria: NR	**12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Rehman, Ismail, Naing, et al., 2007 **#221**	Geographical location: Kelantan, Malaysia Study dates: NR Funding source: Intensification of Research in Priority Areas (IRPA), Ministry of Health, Malaysia Interventions: - Losartan 50 mg daily (n = 19) - Perindopril 4 mg daily (n = 20) Blood pressure was assessed every month and dose of antihypertensive was increased to achieve a target blood pressure of 140/90 mm Hg Were additional anti-hypertension medications allowed: Yes If Yes to above, was this done: Per protocol: "If required a diuretic (indapamide 1.5) followed by a third antihypertensive was added in a stepwise manner on the subsequent visits." Study design: RCT, parallel-group	Number of patients: N = 39 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 46 - Began treatment: 46 - Completed treatment: 39 - Withdrawals/losses to followup: 7 Age: Mean (SD): 52.78 (7.96) **Sex (n [%]):** Female: NR Male: NR Race/ethnicity (n [%]): NR **Baseline blood pressure:** Losartan Perindopril SBP 151 (13.91) 152 (12.21) DBP 94 (10.37) 92 (7.54) The patients were allowed to rest for 10 to 15 min in supine position to achieve basal body conditions. Systolic and diastolic blood pressure were measured using mercury column sphygmomanometer (Baumanometer, W.A. Baum Co. Inc., Copiague, New York) according to JNC VI guidelines.	**1) Blood pressure:** Month 0 – Month 4 changes: Losartan p value Perindopril p value SBP 14 (15.97) 0.002 18 (12.26) < 0.001 DBP 8 (8.54) 0.001 9 (6.23) < 0.001 PP 5 (12.34) 0.077 9 (11.15) 0.002 PWV 0.83 (1.19) 0.007 0.57 (1.22) 0.047 PWVa 0.82 (1.18) 0.042 0.57 (1.22) 0.043 Comparisons between groups were NS 72% achieved target blood pressure of 140/90 mm Hg The remaining 28% of the subjects were equally distributed in the two treatment arms **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR	**General comments:** - May not have used true randomization based on statement, "The ratio of subjects studied in each arm was kept equal" - Small study did not detect differences between groups so may suffer from Type 2 error - Moderate dropout (15%) - Completer analysis only - ITT analysis not stated - Double-blinded - Groups equal at baseline and treated equally Quality assessment: Overall rating: Fair Comments: See General comments, above **Applicability:** - Recruitment not described - Took place in Malaysia - Excluded patients with A1166C polymorphism (not reported how common this is)

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: 2-week washout at start of trial Duration of treatment: 4 months Duration of post-treatment followup: NA	**Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: - Mild to moderate hypertension without evidence of cardiovascular complications - All subjects were homozygous for AT1R A1166C polymorphism (wild type) Exclusion criteria: - Hypertensive target organ damage, acute infection, respiratory or endocrine illness, renal, or hepatic dysfunction - Presence of A1166C polymorphism - Previously treated with either an ACEI or an ARB - On treatment with lipid-lowering drugs, psychotropic agents, antidepressants, nonsteroidal inflammatory drugs, steroids, or hormones - Severe or secondary hypertension, severe hyperlipidemia (total cholesterol >7.5 mmol/L) or other factors that made measurement of PWV technically difficult such as body mass index (BMI) > 35 kg/m^2, atrial fibrillation, peripheral	**7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		vascular disease, and hematocrit < 30 or > 50 g/dL		
Robles, Angulo, Grois, et al., 2004 **#1610**	Geographical location: Badajoz, Spain Study dates: NR Funding source: NR Interventions: - Irbesartan 150 mg/day (n = 15) - Fosinopril 20 mg/day (n = 15) After 4 weeks: If BP ≥ 140/90 titrated by adding 12.5mg/day After 8 weeks: Non-controlled patients excluded Sodium intake limited Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: NR - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: After withdrawal of any antihypertensive therapy, if needed, eligible patients entered a 2-week washout phase Duration of treatment: 12 weeks	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 30 - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR Age: Mean: 61.3 yr Median: NR Range: NR **Sex (n [%]):** Female: 15 Male: 15 Race/ethnicity (n [%]): NR **Baseline blood pressure:** Method of assessment NR Irbesartan / Fosinopril SBP: 157.7 ± 11.2 / 147.9 ± 11.7 DBP: 94.1 ± 5.6 / 92.3 ± 6.3 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria:	**1) Blood pressure:** BP at 12 wk (method of assessment NR; p < 0.001 for all comparisons vs. baseline): Irbesartan / Fosinopril SBP: 131.0 ± 8.7 / 132.2 ± 12.4 DBP: 82.7 ± 4.2 / 84.0 ± 5.4 **2) Rate of use of a single antihypertensive agent for BP control:** HCTZ was added to 6 pts with inadequate BP control at 4 wk (3 in Irb gp) and 8th wk (2 in Irb gp and 1 in Fos gp) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR	**General comments:** None Quality assessment: Overall rating: Fair Comments: - Setting and some of the subjects not described **Applicability:** - Primary objective: effect of drugs on hematopoiesis - Setting and some of the subjects not described

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Duration of post-treatment followup: NA	- Mild or moderate essential HTN (BP ≥ 140/90 and < 180/100) Exclusion criteria: - Creatinine ≥ 1.5 mg/dL - Unstable angina - MI/stroke in last 3 mo - Heart failure - Hypokalemia - COPD - Hematological disease - Hb ≤ 13 gm or >17 gm - Hypersensitivity to test drugs - Pre-menopausal women	**13) Proteinuria:** NR	
Roca-Cusachs, Oigman, Lepe, et al., 1997 **#1611**	Geographical location: Multicenter, with sites in Spain, Austria, Brazil, Czech Republic, China, Colombia, Croatia, Dominican Republic, Ecuador, Jamaica, Mexico, Pakistan, Peru, Russia, Slovak Republic, Slovenia, Taiwan, Ukraine, UAE Study dates: NR Funding source: Merck & Co Interventions: - Losartan 50-100 mg (n = 192) - Captopril 25 mg twice daily-50 mg twice daily (n = 204) Dose titration and co-interventions: Titrated to higher dose at 6 wk if seated DBP ≥ 90; no other antihypertensives allowed Study design:	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 396 - Began treatment: 396 - Completed treatment: 356 - Withdrawals/losses to followup: 40 (17 due to AEs, 7 lost to followup, 7 insufficient response, 7 protocol violations, 2 uncooperative) Age: Mean (SD): 51.4 (10.9) Median: NR Range: NR **Sex (n [%]):** Female: 174 (44%) Male: 222 (56%) Race/ethnicity (n [%]): Black: 36 (9%) Non-black: 360 (91%)	**1) Blood pressure:** Main results in Figure 1 (change in seated DBP) and Figure 2 (change in seated SBP), but mean posttreatment BP values NR in tables or text. Mean change in seated BP from baseline to 12 wk: Losartan (n = 190) / Captopril (n = 203) / P-value SBP: -15.4 / -12.2 / = 0.023 DBP: -11.5 / -9.3 / = 0.010 BP control rates at 12 wk (DBP < 90 or decrease in DBP from baseline of ≥ 10 mm Hg): Losartan: 60.0% Captopril: 54.7% p > 0.10 **2) Rate of use of a single antihypertensive agent for BP control:** NA (no other antihypertensives allowed)	**General comments:** - Patients withdrawn if DBP not ≥ 95 during placebo run-in period resulting in some potential exclusions - Primary outcome was change in DBP/SBP, but one wonders if this was established a priori since final SBP/DBP are not reported in study. Quality assessment: Overall rating: Fair Comments: - Numbers screened and eligible NR **Applicability:** - Minimal racial diversity (91% Caucasian) - Recuitment setting(s) not described - Minimal comorbities in study population; difficult to extrapolate

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: 1-wk drug washout; 4-wk placebo run-in Duration of treatment: 12 wk Duration of post-treatment followup: NA	**Baseline blood pressure:** Trough seated BP assessed using mercury sphygmomanometer after 5-min rest; average of 3 readings Losartan / Captopril SBP 158.2 ± 16.5 / 157.2 ± 16.7 DBP 103.9 ± 6.5 / 103.2 ± 7.1 **Concurrent medications (n [%]):** Other BP meds not permitted **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: - Adult male and female outpatients - Mild-to-moderate HTN (DBP 90-115 before placebo, then 95-115 after 2 & 4 wks on placebo during run-in - No concurrent medical conditions - No therapy that might affect BP Exclusion criteria: - Malignant or secondary HTN - Untreated thyrotoxicosis or hypothyroidism - Significant cardiovascular, cerebrovascular, hepatic, renal, GI, hematologic, pulmonary, or neurologic disorders	**3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Losartan (n = 192) / Captopril (n = 204) ≥ 1 clinical AE 63 (33%) / 83 (41%) ≥ 1 drug-related clinical AE 20 (10%) / 27 (13%) ≥ 1 serious clinical AE 4 (2%) / 10 (5%) Withdrawn due to clinical AEs 5 (3%) / 12 (6%) ≥ 1 laboratory AE 24 (13%) / 24 (12%) ≥ 1 drug-related laboratory AE 11 (6%)* / 3 (2%) * p = 0.029; all other between-group comparisons NS Withdrawals for serious clinical AEs included 1 losartan for encephalopathy and HTN crisis, 1 captopril for HA with TIA and hemiparesis. Other withdrawals were "considered unrelated to study treatment." Withdrawals for clinical AEs included 3 losartan for urticaria + pruritis, chest pain, taste perversion (first 2 related to study treatment); 9 captopril for pruritis, headache (2), vomiting, taste loss, dizziness with headache, rash, dyspnea with heart failure, anxiety with tachycardia (all but last one considered drug-related).	to the general population

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Uncontrolled diabetes - Concurrent disease that would preclude participation or survival (e.g., AIDs or neoplasm) - Alcohol or drug abuse - Clinically significant lab values outside normal range (e.g., serum K < 3.5 or > 5.5 mol/L - Women who were pregnant or lactating - Known sensitivity to captopril or other ACEIs - Concomitant therapy with other investigational drugs, beta-blockers, steroids, ACTH, or lithium	Laboratory AEs included: losartan (increased ALT in 4, hyperbilirubinemia in 2, increased serum creatinine in 2, increased BUN in 1, hyperkalemia in 1); captopril (1 drug-related hyperuricemia and 1 hyperkalemia). **6) Specific adverse events:** Losartan (n = 192) / Captopril (n = 204) Headache: 8% / 10% Cough: 6% / 7% **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** see above **13) Proteinuria:** NR	
Rosei, Rizzoni, Muiesan, et al., 2005 **#1612**	Geographical location: Italy Study dates: NR Funding source: Takeda Italia Farmeceutici S.p.A., Rome, Italy Interventions: - Candesartan 8-16 mg (n = 66)	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 129 - Began treatment: 129 - Completed treatment: 118 - Withdrawals/losses to followup: 11	**1) Blood pressure:** Mean BP at 24 weeks (from Abstract; not clear whether taken using sphygmomanometer [see Figure 1] or automatic device [see Figure 2]): Candesartan: 132/82 ± 12/7 mm Hg Enalapril: 131/85 ± 14/6 mm/Hg p = NS	**General comments:** None Quality assessment: Overall rating: Fair Comments: - Assembly of patients not described

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Enalapril 10-20 mg (n = 63) Dose titration/co-interventions: Patients started on lower dose of study drug; moved to higher dose if BP ≥ 130/85 after 6 wk. If BP still uncontrolled after 12 wk, HCTZ 12.5 mg added. If BP not controlled at 18 wk, HCTZ increased to 25 mg. Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: NR Baseline/run-in period: 2-wk placebo run-in Duration of treatment: 24 wk Duration of post-treatment followup: NA	Age: Mean (SD): 58.4 Median: NR Range: 30 to 70 **Sex (n [%]):** Female: 36% Male: 64% Race/ethnicity (n [%]): NR **Baseline blood pressure:** Seated trough BP measured after 5-min rest; mean of 3 measurements taken at 1-min intervals BP measured using a mercury sphygmomanometer *and* a validated automatic device (Omron 705 CP) Baseline mean values NR (from Abstract; see also Figures 1 and 2): Candesartan: 148/90 ± 11/8 mm Hg Enalapril: 148/91 ± 12/8 mm Hg **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** Candesartan/Enalapril: No alcohol: 49%/52% No smoking: 83%/75% Retinopathy: 6%/3% Heart disease: 9%/13% Kidney disease: 2%/3%	BP response rates at 24 wk (response not defined): Candesartan: 70.5% Enalapril: 71.9% p = NS **2) Rate of use of a single antihypertensive agent for BP control:** Monotherapy at 18-24 weeks: Candesartan: 59% Enalapril: 63.8% **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Any AEs: Candesartan: 27/66 (40.9%) Enalapril: 31/63 (49.2%) p = NS 1 non-drug-related serious AE (diabetes decompensation in patient in candesartan group) **6) Specific adverse events:** NR **7) Persistence/adherence:** Mean compliance: Candesartan: 98.2 ± 13.16% Enalapril: 97.8 ± 13.67% **8) Lipid levels:** Triglycerides (mg/dL): Candesartan (n = 60) Enalapril (n = 57)	**Applicability:** - Patient identification, study site not clear - All patients had NIDDM

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Baseline 145.5 ± 79.5 143.9 ± 111.5 24 wk 159.1 ± 95.3 154.8 ± 160.5	
		Recruitment setting: NR Inclusion criteria: - Grade 1 essential hypertension (SBP 140-159; DBP diastolic 90-99) at the end of 2-wk run-in period - Age 30-70 yr - Previous diagnosis of NIDDM with or without hypoglycemic therapy - Previously treated with antihypertensive drugs (including ACEs or ARBs) for ≤ 1 mo in the 3 mo preceding enrollment - If previously treated, enrolled only if did not tolerate or respond to previous antihypertensive medication Exclusion criteria: - Secondary hypertension - SBP > 159, DBP > 99 - IDDM, intolerance or contraindications to study drugs - Use of study drug within 4 wk of enrolment - Major cardiac arrhythmias, hemodynamically relevant valvular heart disease, AV blocks grade 2 or 3 - CHF (NYHA II-IV) - MI, stroke, coronary surgery, TIA within previous 3 mo - Angina - Autonomic neuropathy - PVD with lesions - Known renal artery stenosis, kidney transplantation	Total cholesterol (mg/dL): Candesartan (n = 60) Enalapril (n = 57) Baseline 212.8 ± 39.4 221.2 ± 37.0 24 wk 210.0 ± 35.4 228.1 ± 37.3 LDL cholesterol (mg/dL): Candesartan (n = 60) Enalapril (n = 57) Baseline 142.4 ± 34.8 152.0 ± 35.5 24 wk 140.9 ± 28.8 157.5 ± 34.9 **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** No difference (data not reported) **13) Proteinuria:** Candesartan: 33.9 (92.6) Enalapril: 58.3 (195.3)	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td></td><td>- Serum creatinine > 1.6 mg/dL
- Severely impaired liver function, serum sodium ≤ 130 mmol/L, serum K ≤ 3.6 mmol/L</td><td></td><td></td></tr>
<tr><td>Ruff, Gazdick, Berman, et al., 1996

#1614</td><td>Geographical location: 12 centers in the U.S.

Study dates: NR

Funding source: NR, but authors from Merck

Interventions:
- Losartan 50 mg daily; therapy intensified at 2-wk intervals for DBP ≥ 90 (see below) (n = 50)
- Enalapril 20 mg daily; therapy intensified at 2-wk intervals for DBP ≥ 90 (n = 25)

Titration protocol:
1) Double dose of study med
2) Add hctz 25mg daily
3) Add atenolol 50 mg daily and titrate to 100 mg daily or add dihydropyridine calcium channel blocker
4) Add other therapy at discretion of investigator

Study design:
RCT, parallel-group

Blinding:
- Patients: Yes (double-dummy)
- Providers: Yes
- Assessors of outcomes: NR

Was allocation concealment</td><td>Number of patients:
- Screened for inclusion: NR
- Eligible for inclusion: NR
- Randomized: 75 (2:1 losartan:enalapril)
- Began treatment: 75
- Completed treatment: 67
- Withdrawals/losses to followup: 8

Age:
Mean (SD): 50.9 (11.6)
Median: NR
Range: 23-74

Sex (n [%]):
Female: 30 (40%)
Male: 45 (60%)

Race/ethnicity (n [%]):
White- 40 (53%)
Black- 32 (43%)
Hispanic – 2 (3%)
Native American – 1 (1%)

Baseline blood pressure:
Trough seated BP measured using a standard mercury sphygmomano-meter after 5 min rest; average of 3 readings taken at 1-min intervals
<u>Losartan</u> <u>Enalapril</u>
SBP
173.7 ± 14.5 176.5 ± 14.9
DBP</td><td>1) Blood pressure:
Seated trough BP:
<table><tr><td></td><td>Los-pre</td><td>Los-12 wk</td><td>Enal - pre</td><td>Enal - 12 wk</td></tr><tr><td>SBP</td><td>173.7 (14.5)</td><td>140.3 (16.1)</td><td>176.5 (14.9)</td><td>133.8 (14.5)</td></tr><tr><td>DBP</td><td>118 (3.6)</td><td>90.8 (8.7)</td><td>119 (3.1)</td><td>88.4 (5.1)</td></tr></table>All pre-post differences significant at P < 0.05
Diff in SBP between losart and enal (p = 0.037)
Diff in DBP between losart and enal (p = 0.051)

BP response: By 12 wk, 98% of losartan patients and 100% of enalapril patients had a DBP < 90 or a reduction of DBP ≥ 10 (between-group difference not significant)

Subgroup analysis reported for black vs. non-black.
“Similar reductions in black compared with non-black patients”

SBP:<table><tr><td></td><td colspan="2">Non-black</td><td colspan="2">Black</td></tr><tr><td></td><td>Losart</td><td>Enal</td><td>Losart</td><td>Enal</td></tr><tr><td>Pre-</td><td>172.5 (15.4)</td><td>180.3 (15.3)</td><td>175.2 (13.6)</td><td>170.9 (12.9)</td></tr><tr><td>Post-</td><td>141.5 (16.8)</td><td>135.4 (14.9)</td><td>138.6 (15.8)</td><td>131.4 (14.2)</td></tr><tr><td>Change</td><td>-31.0</td><td>-44.9</td><td>-36.6</td><td>-39.5</td></tr></table></td><td>General comments:
- Main limitation is lack of description of numbers screened and eligible

Quality assessment:
Overall rating: Good

Applicability:
- Exclusion criteria limit the applicability to a larger hypertension population
- Short time frame
- Non-meaningful endpoints beyond BP response and tolerability</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

adequate?: NR

Baseline/run-in period: 2- to 7-day baseline washout. No run-in period

Duration of treatment: 12 wk

Duration of post-treatment followup: NA

118 ± 3.5 119 ± 3.1

Seated response peak BP also collected (5-8 hr after administration)

Concurrent medications (n [%]):
Antihypertension meds stopped at baseline. No other meds reported.

Comorbidities (n [%]): NR

Recruitment setting: 12 US centers (no other info)

Inclusion criteria:
- Sitting trough DBP 115-130

Exclusion criteria:
- Females of childbearing potential were included only w/ neg preg test w/I 72yrs and monthly thereafter
- DM if fasting sugar >180
- Secondary htn
- Serious heart, liver, or renal disease
- Any other active medical condition or tx that might affect bp or confound results of study
- ASA, acetaminophen, nsaids and low dose TCAs had to be OK'd by study monitor

	(16.2)	(16.6)	(19.5)	(20.0)

DBP:

	Non-black		Black	
	Losart	Enal	Losart	Enal
Pre-	118.2 (3.2)	118.6 (2.5)	118.9 (3.9)	120.3 (3.7)
Post-	91.1 (10.0)	88.2 (4.4)	90.5 (6.9)	88.7 (6.2)
Change	-27.1 (8.9)	-30.4 (4.9)	-28.4 (6.8)	-31.6 (5.0)

2) Rate of use of a single antihypertensive agent for BP control:
At week 12:
3/50 in losartan group (6%)
4/25 in enalapril group (16%)

3) Mortality: NR

4) Morbidity: NR

5) Safety:

	Losartan (n = 50)	Enalapril (n = 25)
Adverse event	35 (70%)	19 (76%)

6/50 pts withdrew from losartan
2/25 pts withdrew from enalapril

6) Specific adverse events:

	Losartan (n = 50)	Enalapril (n = 25)
Headache	22%	20%
Dizziness	14%	12%
Edema	4%	12%

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Cough 8% 12% **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Ruilope, Jager, and Prichard, 2001 **#1615**	Geographical location: 48 centers in France, Germany, Ireland, The Netherlands, Spain, Sweden, and UK Study dates: NR Funding source: NR, but contact author employed by Solvay Pharma Interventions: - Eprosartan 600 mg qd (titrated to 800 mg qd after 3 wk if SBP > 140 mm Hg) (n = 168) - Enalapril 5 mg qd (titrated to 10, then 20 q 3 wk if SBP > 140 mm Hg) (n = 163) Study design: RCT, parallel-group Blinding:	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: 396 - Randomized: 334 - Began treatment: 334 - Completed treatment: 290 - Withdrawals/losses to followup: NR; 3 patients had no valid efficacy data and were excluded from analysis; reasons for other discontinuations NR - Population analyzed = 331 (eprosartan 168, enalapril 163) Age: Mean (SD): 73 Median: NR Range: NR **Sex (n [%]):** Female: 181 (54%) Male: 153 (46%)	**1) Blood pressure:** Mean post-treatment BP values NR Mean changes from baseline (at 12 wk): Eprosartan / Enalapril / P-value Sit SBP -18.0 / -17.4 / 0.76 Sit DBP -9.4 / -9.6 / 0.84 Response rates (Sit SBP < 140 or 140-150 with decrease of ≥ 20 mm Hg from baseline; Sit DBP < 90 or 90-100 with decrease of ≥ 10 mm Hg from baseline); last available BP reading used: Eprosartan / Enalapril SBP 68/168 (41%) / 63/163 (39%) DBP 108/68 (64%) / 111/163 (68%) **2) Rate of use of a single antihypertensive agent for BP control:**	**General comments:** None Quality assessment: Overall rating: Good Comments: Enalapril dose not comparable to eprosartan. **Applicability:** - Multinational, but virtually all Caucasian subjects

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Patients: Yes - Providers: Yes - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: Single-blind, placebo run-in 3-4 wks Duration of treatment: 12 weeks Duration of post-treatment followup: 7-10 days after treatment period	Race/ethnicity (n [%]): Caucasian 332 (99%) **Baseline blood pressure (± SEM):** Trough BP measured 3 times at 2-min intervals after patient seated for at least 5 min using mercury or mercury-calibrated sphygmomano-meter; mean of 3 readings used Eprosartan / Enalapril Sit SBP 176 ± 0.9 / 175 ± 0.9 Sit DBP 98 ± 0.4 / 98 ± 0.4 **Concurrent medications (n [%]):** Any medication: Eprosartan: 69% Enalapril: 75.5% Other antihypertensive medication: Eprosartan: 8.8% Enalapril: 6.7% **Comorbidities (n [%]):** NR **Recruitment setting:** Not described Inclusion criteria: - Age ≥ 65 years - Essential HTN - Sitting SBP ≥ 160 mmHg and DBP 90-114 mmHg - Newly diagnosed or requiring	Other antihypertensive medication taken during trial: Eprosartan: 8.8% Enalapril: 6.7% **3) Mortality:** 2 deaths, one in each group; neither was considered related to study medication **4) Morbidity:** NR **5) Safety:** Eprosartan / Enalapril ≥ 1 AE 61 (35.7%) / 83 (50.9%) Susp/prob. AE 11 (6.4%) / 24 (14.7%) **6) Specific adverse events:** Eprosartan / Enalapril Headache (4.1%) / 10 (6.1%) Fatigue (2.9%) / 7 (4.3%) Diarrhea (2.9%) / 3 (1.8%) Injury (2.3%) / 2 (1.2%) Abdominal pain (2.5%) / 3 (1.8%) Dizziness (1.8%) / 5 (3.1%) Infection viral 5 (3.1%) / 2 (1.2%) Coughing (0.6%) / 10 (6.1%) UTI 0 (0%) / 5 (3.1%)	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		change in treatment due to poor efficacy or tolerability Exclusion criteria: - Secondary HTN - Advanced hypertensive retinopathy - Sitting SBP > 210 mm Hg - MI or CVA < 90 days - CHF, angina - Poorly controlled diabetes - Significant renal or hepatic disease - Significant ventricular tachyarrhythmias -Severe disease (e.g., cancer) which could preclude participation or survival - Alcohol or drug abuse - Recent use of investigational drug - Concurrent use of MAOIs, tricyclics, phenothiazine derivatives, any medication know to affect BP, or sympathomimetic amines	**7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Saito, Asayama, Ohkubo, et al., 2004 **#1616**	Geographical location: Japan (nationwide) Study dates: 2002 - Mar 2003 Funding source: Non-profit foundation, device manufacturers Interventions: CCB (n = 239) ACEI (n = 214) ARB (n = 200)	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: 1736 - Randomized: 1086 - Began treatment: NR - Completed treatment: 653 - Withdrawals/losses to followup: 433 had not completed ≥ 6 mo followup Age: Mean (SD): NR Median: NR	**1) Blood pressure:** Home values at 6 mo, measured using automated device: SBP / DBP CCB 134 ± 12 / 82 ± 10 ACEI 136 ± 15 / 80 ± 10 ARB 134 ± 13 / 80 ± 9 **2) Rate of use of a single antihypertensive agent for BP control:** At 6 months: CCB: 34% (82/239)	**General comments:** - BP data from home monitoring, may not be comparable to clinic-based seated measurements - Rates of discontinuation and switching driven by protocol, rather than usual care, may be more reliable Quality assessment: Overall rating: Fair Comments:

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td>Study design: RCT, parallel-group

Blinding:
- Patients: No
- Providers: No
- Assessors of outcomes: Yes

Was allocation concealment adequate?: Yes

Baseline/run-in period: None

Duration of treatment: 6 mo

Duration of post-treatment followup: NA</td><td>Range: NR

Sex (n [%]):
Female: NR
Male: NR

Race/ethnicity (n [%]): NR
(presumably 100% Japanese)

Baseline blood pressure:
Home BP measured using automated device (Omron HEM-747IC-N)

<u>SBP</u> <u>DBP</u>
CCB
149 ± 14 90 ± 10
ACEI
150 ± 14 89 ± 11
ARB
149 ± 13 89 ± 10

Concurrent medications (n [%]):
0 [0%]

Comorbidities (n [%]): NR

Recruitment setting: Primary care practice

Inclusion criteria:
- Previously untreated patients ≥ 40 years of age
- Home BP values ≥ 135/85 mmHg

Exclusion criteria: NR</td><td>ACEI: 24% (51/214)
ARB: 30% (60/200)

3) Mortality: NR

4) Morbidity: NR

5) Safety: NR

6) Specific adverse events: NR

7) Persistence/adherence:
At 6 months, switches determined by BP values and computerized treatment algorithm:
<table><tr><td>Drug</td><td>Continued</td><td>Switched</td><td>D/c’d</td></tr><tr><td>ARB</td><td>89%</td><td>9%</td><td>2%</td></tr><tr><td>ACEI</td><td>71%</td><td>28%</td><td>1%</td></tr><tr><td>CCB</td><td>89%</td><td>8%</td><td>3%</td></tr></table>8) Lipid levels: NR

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: NR

11) LV mass/function: NR

12) Creatinine/GFR: NR

13) Proteinuria: NR</td><td>- Complicated treatment/switching algorithm
- Drug intervention nested within what seems to primarily by a health services intervention
- See above, under General comments

Applicability:
- Japanese ethnic population may not be generalizable to U.S.</td></tr>
<tr><td>Sanchez, Masnatta,</td><td>Geographical location: Buenos Aires, Argentina</td><td>Number of patients: N = 34
- Screened for inclusion: 42</td><td>1) Blood pressure:
3 months:</td><td>General comments:
Comparison of treatment focused</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Pesiney, et al., 2008 **#1200**	Study dates: NR Funding source: NR Interventions: - Ramipril 10 mg daily (n = 34) - Telmisartan 80 mg daily (n = 34) Were additional anti-hypertension medications allowed: No Study design: RCT, crossover Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: NR Baseline/run-in period: 2 weeks Washout period(s): 2 weeks Duration of treatment: 3 months (and then 3 months after washout and crossover) Duration of post-treatment followup: None	- Eligible for inclusion: 34 - Randomized: 34 - Began treatment: 34 - Completed treatment: 34 - Withdrawals/losses to followup: 0 Age: Mean (SD): NMHT 32 ± 5 MHT 34 ± 4 NMHT = non-modulating hypertensive MHT = modulating hypertensive **Sex (n [%]):** Female: 15 (44.1%) Male: 19 (55.9%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Blood pressure values were the mean value of three consecutive measurements, elapsed by 1 min, performed in each patient at the end of each of the above conditions. Ramipril: NMHT 162 ± 12, 97 ± 4 MHT 159 ± 10, 102 ± 4 Telmisartan NMHT 161 ± 9, 96 ± 5 MHT 154 ± 8, 96 ± 5 **Concurrent non-hypertension medications (n [%]):** None allowed	Ramipril: NMTH 139 ± 7, 89 ± 2 MTH 142 ± 6, 93 ± 3 Telmisartan: NMTH 137 ± 5, 86 ± 3 MTH 137 ± 6, 88 ± 4 All were $p < 0.05$ compared to baseline Article states that SBP and DBP were similarly reduced by the two interventions **2) Rate of use of a single antihypertensive agent for BP control:** 100% **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** Telmisartan improved the triglyceride level in both MHT and NMHT patients compared with both baseline values and ramipril **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** In MHT patients, after 3 months treatment with either ramipril or telmisartan no changes were found in fasting and 120min glycemia or insulemia	on high renin nonmodulating salt-sensitive hypertensives Quality assessment: Overall rating: Fair Comments: - Randomized - Complete followup of all enrolled patients - Similar treatment for 2 interventions other than medication - Objective outcomes (except maybe BP) done rigorously - Not blinded - Baseline characteristics not reported for telmisartan vs. ramipril groups **Applicability:** Focuses on NMHT versus MHT patients

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Comorbidities (n [%]): NR **Recruitment setting:** Outpatient clinic Inclusion criteria: - Essential HTN seen in the outpatient clinic - Normal renal function Exclusion criteria: - Secondary HTN (by history and physical examination, screening biochemical testing, renal echography and nuclear resonance or renal arteriography) - Failure to complete 10-day period of salt intake or in compliance to the daily sodium intake	In NMHT patients, telmisartan after 3 months treatment significantly reduced fasting and 120 min insulinemia (fasting 8.4 ± 2, 120 min 25 ± 10 uU% $p < 0.01$) compared to either baseline values or ramipril treatment Telmisartan improved the HOMA-IR index in both MHT and NMHT patients compared with both baseline values and ramipril **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Sato, Tabata, Hayashi, et al., 2003 **#1617**	Geographical location: Ibaraki, Japan Study dates: NR Funding source: NR Interventions: Cross sectional cohort of patients treated with: - Trandolapril (n = 18) - Enalapril (n = 5) or - Candesartan (n = 26) If BP not controlled (< 130/85 mm Hg), then calcium antagonist, α1-blocker, and central-acting α2-stimulant	Number of patients: 49 (cross-sectional cohort) Age: Mean (SD): 63.3 Median: NR Range: NR **Sex (n [%]):** Female: 23 (47%) Male: 26 (53%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Seated BP measured using a mercury sphygmomanometer after 15-min rest (average of 3	**1) Blood pressure:** NR separately for hypertensive patients **2) Rate of use of a single antihypertensive agent for BP control:** NR separately for hypertensive patients **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** ACEI: cough 2 patients No other clinical AEs observed **7) Persistence/adherence:** NR	**General comments:** - 15/49 subjects (30.6%) were normotensive; limited results reported separately for hypertensive subjects Quality assessment: Overall rating: Poor Comments: - Results not separated by hypertension status - Cross-sectional without establishment of an inception cohort **Applicability:** - Limited to a single hospital in

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	added successively Study design: Cross-sectional cohort study Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: NA Baseline/run-in period: NA Duration of treatment: NA (patients were treated previously with ACEI or ARB for 11 ± 3 months) Duration of post-treatment followup: NA	readings) Note: 15/49 patients (30.6%) normotensive Mean baseline BP values: ACEI ARB SBP 141 ± 13 142 ± 16 DBP 78 ± 11 79 ± 9 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** See Inclusion criteria **Recruitment setting:** Single hospital Inclusion criteria: - Clinical diagnosis of diabetic nephropathy stage 2 or 3A (defined by presence of either micro-albuminuria with urinary albumin excretion [UAE] 30-300 mg/g creatinine [stage 2] or overt proteinuria [UAE > 300 mg/g creatinine] with a glomerular filtration rate > 60 mL/min [stage 3A]) Exclusion criteria: None specified	**8) Lipid levels:** NR separately for hypertensive patients **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR separately for hypertensive patients **11) LV mass/function:** NR (LVMI not reported by treatment/hypertension status) **12) Creatinine/GFR:** NR separately for hypertensive patients **13) Proteinuria:** Mean changes in urinary albumin excretion (± SEM, mg/g creatinine), hypertensive patients only: ACEI (n = 16) ARB (n = 18) Before 417 ± 162 455 ± 166 After 92 ± 37 99 ± 52	Japan - All patients had diabetic nephropathy stage 2 or 3A
Scaglione, Argano, Di Chiara, et al., 2007 **#214**	Geographical location: Palermo, Italy Study dates: NR Funding source: Project grant (60%) from University of Palermo	Number of patients: N = 57 - Screened for inclusion: 328 consecutive hypertensive patients - Eligible for inclusion: NR - Randomized: 57 - Began treatment: 57	**1) Blood pressure:** Losart Rami Comb SBP, mmHg 133 ± 5* 134 ± 5* 131 ± 6* DBP, mm Hg 82 ± 7* 81± 8* 78 ± 8* *P < 0.05 vs. baseline Losart Rami Comb	**General comments:** - Small study - Stratified (matched) randomization - Complete followup on all patients - ITT analysis - Groups similar at baseline and

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	(Italy) Interventions: - Losartan 50 mg/day (n = 19) - Ramipril 5 mg/day (n = 19) - Combination of losartan 50 mg/day plus ramipril 5 mg/day (n = 19) Were additional anti-hypertension medications allowed: Yes If Yes to above, was this done: Per protocol: HCTZ (12.5 mg once daily) was added to achieve BP < 140/90 (3 total, one per group) Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: Yes Baseline/run-in period: NA Duration of treatment: 24 weeks Duration of post-treatment followup: NA	- Completed treatment: 57 - Withdrawals/losses to followup: 0 Age: Mean (SD): 55.67 (7.34) **Sex (n [%]):** Female: 27 (47.4%) Male: 30 (52.6%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** SBP/DBP: Losartan: 162 ± 7/94 ± 6 Ramipril: 159 ± 7/98 ± 9 Combo: 161 ± 8/94 ± 12 Sitting BP was measured three times with an interval of about 2 min, and the mean was calculated **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** **A**ntihypertensive centre of the Department of Internal Medicine, University of Palermo (Italy) Inclusion criteria: SBP 140-179 mmHg and/or DBP 90-109 mmHg Exclusion criteria: - Any form of	TGFb1 (ng/ml) 4.1 ± 4.8 3.1 ± 3.1 6 ± 3.4*† DTGFb1 (%) 48 ± 28 42 ± 29 80 ± 12*† $\Delta LVM/h^{2.7}$ ($g/m^{2.7}$) 6.4 ± 5 8.5 ± 8.5 14 ± 7‡§ $\Delta LVM/h^{2.7}$ (%) 14 ± 9 16 ± 16 24 ± 15‡§ ΔSBP (mm Hg) 29 ± 9 25 ± 12 30 ± 11 ΔSBP (%) 18 ± 5 16 ± 7 19 ± 6 ΔDBP (mm Hg) 14 ± 9 17 ± 11 17 ± 12 ΔDBP (%) 14 ± 11 18 ± 10 17 ± 12 ΔMBP (mm Hg) 16 ± 8 18 ± 9 21 ± 11 ΔMBP (%) 14 ± 7 15 ± 7 18 ± 8 *P < 0.03 vs. losartan †P < 0.0001 vs. ramipril ‡P< 0.05 vs. losartan §P < 0.03 vs. ramipril Patients with LVH at baseline: Losart Rami Comb $DLVM/h^{2.7}$ (%) -16 ± 4 -19 ± 5 -27 ± 5†‡ †P < 0.02 vs. ramipril; ‡P < 0.01 vs. losartan **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** See immediately below **6) Specific adverse events:** “Two patients complained of asthenia, two of cough and three of dizziness but treatments were not discontinued.” (treatment assignments NR)	treated similarly Quality assessment: Overall rating: Good **Applicability:** - Small trial in Italy recruiting from hypertension center - Other BP drugs and comorbidities either not allowed or not reported

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		secondary hypertension - Stage III essential hypertension - Any irreversible end organ damage owing to arterial hypertension - Metabolic bone disease - Hyperthyroidism - Cardiovascular disease - Diabetes - Dyslipidemia - Hepatic disease - Alcoholic liver disease - Malignancy	**7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** See table under outcome 1, above **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Schieffer, Bunte, Witte, et al., 2004 **#1618**	Geographical location: Hanover and Hamburg, Germany Study dates: NR Funding source: Sanofi-Synthelabo Interventions: - Enalapril 2 x 10 mg/day (gp A, ENAL) (n = 27) - Irbesartan 2 x150 mg/day (gp B, IRB) (n = 21) Study design: RCT, parallel-group Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: NR Was allocation concealment	Number of patients: - Screened for inclusion: 60 - Eligible for inclusion: - Randomized: 48 - Began treatment: 48 - Completed treatment: 47 - Withdrawals/losses to followup: 1 (enalapril; symptomatic hypotension); a further 11 patients were excluded from the analysis due to protocol violations Age: Mean (SD): 57.1 (weighted average) Median: NR Range: NR **Sex (n [%]):** Female: 12 Male: 36	**1) Blood pressure:** At 3 months (method of assessment NR): Enalapril / Irbesartan SBP: 133 ± 19* / 133 ± 22* DBP: 83 ± 9** / 80 ± 12** * p < 0.01 vs. baseline ** p < 0.05 vs. baseline **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR	**General comments:** None Quality assessment: Overall rating: Poor Comments: - Not clear all patients were hypertensive - No run-in period - LV results not quantified **Applicability:** - Race of patients not described

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	adequate?: Yes (randomization list) Baseline/run-in period: NA Duration of treatment: 3 months Duration of post-treatment followup: NA	Race/ethnicity (n [%]): NR **Baseline blood pressure:** <u>Enalapril</u> <u>Irbesartan**</u> SBP: 147 ± 35 143 ± 23 DBP: 88 ± 16 84 ± 16 Method of assessment NR **Concurrent medications (n [%]):** 1 patient in each group received oral diabetes medication **Comorbidities (n [%]):** 4 patients receiving irbesartan and 6 receiving enalapril had diabetes **Recruitment setting:** NR (university hospital?) Inclusion criteria: - 6-8 weeks after coronary angioplasty - No symptoms of angina or heart failure Exclusion criteria: - Receiving ACE, ARB, HMG-CoA reductase inhibitor, NSAID (100 mg aspirin allowed) - CRF - LDL ser levels >150mg/dL - Hypotension (SBP < 90mm)	**7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** Reported to be no difference between groups (no numerical data reported) **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Schram,	Geographical location: 6 sites in	Number of patients:	**1) Blood pressure:**	**General comments:**

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
van Ittersum, Spoelstra-de Man, et al., 2005 **#1619**	The Netherlands Study dates: July 1998-Oct 2001 Funding source: AstraZeneca Interventions: - HCTZ 12.5 mg (n = 24) - Candesartan 8 mg (n = 24) - Lisinopril 10 mg (n = 22) Dose titration/co-interventions: Target BP = seated BP < 130/85 or SBP decrease > 10% with DBP < 85. If target BP not achieved, then following added consecutively: - HCTZ 12.5 mg - Doubling of study medication - Felodipine 5 mg - Metoprolol 50 mg - Doxazosin 2 mg - Felodipine 5 mg - Metoprolol 50 mg - Doxazosin 2 mg - Felodipine 5 mg - Metoprolol 100 mg - Doxazosin 4 mg Study design: RCT, parallel-group Blinding: - Patients: Yes (double-dummy) - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: NR	- Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 70 - Began treatment: 70 - Completed treatment: 60 - Withdrawals/losses to followup: 10 (9 due to AEs, 1 for unspecified reasons) Age (candesartan and lisinopril groups): Mean (SD): 61.0 Median: NR Range: NR **Sex (candesartan and lisinopril groups; n [%]):** Female: 27/46 (59%) Male: 19/46 (41%) Race/ethnicity (n [%]): 100% Caucasian **Baseline blood pressure:** Seated BP measured after 5 min of seated rest; mean of 3 consecutive measurements) Candesartan (n = 24) / Lisinopril (n = 22) SBP 151± 14 / 149 ± 9 DBP 94 ± 10 / 93 ± 7 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR	Mean seated BP at 12 mo: Candesartan (n = 24) / Lisinopril (n = 22) SBP 133 ± 15 / 132 ± 12 DBP 81 ± 11 / 80 ± 7 p = NS for between-group differences Percentage of patients achieving target BP (seated BP < 130/85 or SBP decrease > 10% with DBP < 85) after titration phase: Candesartan: 67% Lisinopril: 68% **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** None **4) Morbidity:** NR **5) Safety:** Withdrawals due to AEs: Candesartan: 3/24 (12.5%) Lisinopril: 1/22 (4.5%) AEs leading to withdrawal: Candesartan: Palpitations 1; dizziness 1; microalbuminuria 1 Lisinopril: Rise in creatinine 1 **6) Specific adverse events:** NR except AEs leading to withdrawal (see immediately above) **7) Persistence/adherence:** NR **8) Lipid levels:**	- Comparatively complicated treatment protocol with multiple co-interventions ("aggressive antihypertensive therapy") - Pre-study titration phase lasted until target BP achieved or until treatment options exhausted (4-6 mo) Quality assessment: Overall rating: Good **Applicability:** - No mention of site selection; not clear if all sites were hospital-based clinics - All patients had type 2 diabetes - 100% Caucasian study population

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Baseline/run-in period: 1-mo run-in (patients treated with diet only); if on ACEIs, these were withdrawn for 3 months prior to the run-in period Duration of treatment: 4- to 6-mo BP titration period (continued until target BP achieved or until above treatment protocol exhausted), 12-mo study period Duration of post-treatment followup: NA	**Recruitment setting:** Outpatient clinics, newspaper advertisements Inclusion criteria: - Type II diabetes mellitus for ≥ 6 mo - Age 35 to 70 yr - Caucasian ethnicity - Urinary albumin excretion < 100 mg/24 hr Exclusion criteria: - Pregnancy or planned pregnancy - History of MI, angina, coronary artery bypass surgery, angioplasty, stroke, CHF, malignancy, or other serious illness - Serum creatinine > 140 µmol/L - BMI > 35 kg/m^2 - Alcohol and/or drug abuse - Participation in other clinical trials	No change (data not shown) **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** No change in HbA1c (data not shown) **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** Urinary albumin excretion decreased significantly at 12 mo vs. baseline in both groups, with no significant difference between groups (data shown only graphically [Figure 3])	
Sengul, Altuntas, Kurklu, et al., 2006 **#291**	Geographical location: Istanbul, Turkey Study dates: NR Funding source: NR Interventions: Phase I (weeks 1-24) **1)** Telmisartan 80 mg **2)** Lisinopril 20 mg Phase II (weeks 24-52) **1)** Telmisartan 80 mg **2)** Lisinopril 20 mg	Number of patients: Weeks 1-24: N = 219 Weeks 24-52: N = 192 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 219 - Began treatment: 219 - Completed treatment: 192 - Withdrawals/losses to followup: 27 Age: Mean (SD): Weeks 1-24: 56.6 ± 8.3	**1) Blood pressure:** **Phase I (Weeks 1-24):** Telmisartan Lisinopril p value SBP: -10.0 -11.1 p > 0.2 DBP: -5.3 -5.6 p > 0.2 **Phase II (Weeks 24-52):** Telm Lisin Telm+Lis Lis+Telm p SBP: -15.1 -16.4 -25.5 -25.2 0.003 DBP:	**General comments:** Unusual design, but 2 phases allow comparison of ACEI vs. ARB, then longer evaluation of ACEI vs. ARB vs. ACEI/ARB vs. ARB/ACEI. Quality assessment: Overall rating: Fair Comments: - Protocol/measurements clear - Randomization not discussed - Open-label and blinding of

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	3) Telmisartan 80 mg + lisinopril 20 mg **4)** Lisinopril 20mg + telmisartan 80mg Were additional anti-hypertension medications allowed: Yes If Yes to above, was this done: Per protocol Study design: RCT, parallel-group (authors call it "crossover", but they simply add a med for half of each of the 1st 2 treatment groups) Blinding: - Patients: No - Providers: No - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: 2 weeks Washout period(s): No washout during addition of 2nd agent after 24 weeks Duration of treatment: 24 weeks phase I (ACE vs. ARB) + 28 weeks phase II (ACE vs. ARB vs. ACE + ARB); total > 52 weeks Duration of post-treatment	Weeks 24-52: 56.9 ± 8.1 Range: 40-65 **Sex (n [%]):** Female: Weeks 1-24: 137 (62.6%) Weeks 24-52: 119 (62.0%) Male: Weeks 1-24: 82 (37.4%) Weeks 24-52: 73 (38.0%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Assessment: "SBP and DBP were measured in the morning about 24 h after the previous drug administration (trough value) using an automatic device (Omron HEM-705 CP, Omron Electronics, Tokyo, Japan) with the patient having been seated for 10 min. The mean of the three measurements taken at 5-min intervals was recorded. Blood pressure was also measured once after the patient had been standing for 2 min." Phase I (weeks 1-24): n = 109, 11 respectively Telmisartan Lisinopril SBP: 150.4 ± 14.2 151.2 ± 14.4 DBP: 89.9 ± 5.4 87.9 ± 5.2 Phase II (weeks 24-52): n = 48, 4 49, 47, respectively	-10.2 -10.4 -15.4 -15.2 0.003 **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** 15 discontinued lisinopril due to AEs: nausea, stomach upset, respiratory infection, cough, headache, dizziness/ feeling weak 12 discontinued telmisartan due to AEs: nausea, headache, dizziness, stomach upset, cough, GI problems, withdrawal of consent **6) Specific adverse events:** See above **7) Persistence/adherence:** Collected but NR, apart from discontinuations due to AEs **8) Lipid levels:** Measurements: "High-density lipoprotein cholesterol was measured by a precipitation-based method with phosphotungstic acid. Low-density lipoprotein cholesterol was calculated using Friede- wald's formula." Serum LDL cholesterol (mg/dL; ranges available if needed for meta-analyses):	measurements not clear **Applicability:** - All diabetes population with history of microalbuminuria - Turkish population

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	followup: NR	Telmisartan Lisinopril SBP: 140.4 ± 14.0 140.1 ± 13.2 DBP: 84.6 ± 7.0 82.3 ± 6.6 Telm + Lisin Lisin + Telm SBP: 140.2 ± 13.4 139.5 ± 13.0 DBP: 83.4 ± 6.7 82.0 ± 6.5 **Concurrent non-hypertension medications (n [%]):** Phase I (Weeks 1-24): Telmisartan Lisinopril HCTZ n = 19 n = 21 12.5 mg/d Phase II (Weeks 24-52): Telmisartan Lisinopril HCTZ n = 1 n = 10 12.5 mg/d Telm + Lisin Lisin + Telm HCTZ n = 7 n = 8 **Comorbidities (n [%]):** Diabetes 2 n=219 (100%) **Recruitment setting:** NR – appears to be single academic center, Istanbul, Turkey Inclusion criteria: - Previous diagnosis of HTN	Baseline 52 weeks Telmisartan 3.4 3.6 Lisinopril 3.3 3.5 Telm + Lisin 3.5 3.5 Lisin + Telm 3.5 3.4 *p = 0.42 at baseline and p = 0.40 at 52 weeks Serum triglycerides (mmol/L; ranges available if needed for meta-analyses): Baseline 52 weeks Telmisartan 2.2 2.4 Lisinopril 2.4 2.4 Telm + Lisin 2.3 2.5 Lisin + Telm 2.2 2.4 *p = 0.43 at baseline and p = 0.40 at 52 wks **9) Progression to type 2 diabetes:** NA **10) Markers of carbohydrate metabolism/diabetes control:** Authors state “no significant changes in mean values for HgbA1c” **11) LV mass/function:** NR **12) Creatinine/GFR:** Serum creatinine (mmol/L; [95% CI available if needed for meta-analyses; as well as creatinine clearance calculated by the Cockcroft-Gault formula) Baseline 52 weeks Telmisartan	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		(SBP ≥ 140 mmHg or DBP ≥ 90 mmHg), despite receiving ACE inhibitor monotherapy for ≥ 6 months - Microalbuminuria (AER rate 30-300 mg/24 hr for a minimum of 3 consecutive occasions Exclusion criteria: - Type 1 DM - Alcoholism - Thyroid disease - SBP > 200 mmHg - Any non-diabetic cause of secondary HTN - Urinary tract infection - Persistent haematuria - Chronic liver disease - Overt carcinoma - Any cardiovascular event in the previous 6 months - Serum creatinine ≥ 150 mmol/L - Serum potassium ≥ 5.5 mmol/L - Pregnancy	85 82 Lisinopril 86 83 Telm + Lisin 84 84 Lisin + Telm 83 83 *p = 0.41 at baseline and p = 0.35 at 52 wks **13) Proteinuria:** Reduction in abumin excretion rate (AER), measured in mg/24hr: "Microalbuminuria was determined using turbidimetry (Cobas Mira Plus, Roche, Montclaire, NJ, USA) as the geometric mean of AER of three consecutive 24-h urine collections." (95% CI available if needed for meta-analyses.) **Phase I (Weeks 1-24):** Telmisartan Lisinopril p value AER: -80 -98 0.12 **Phase II (Weeks 24-52):** Telm Lisin Telm+Lis Lis+Telm p AER: -92 -107 -136 -139 0.04	
Shand, 2000 **#1620** *and* **Shand and Lynn, 2000** **#1621**	Geographical location: Christchurch, New Zealand Study dates: NR Funding source: Merck Sharp and Dohme Interventions: - Losartan 50-100 mg daily (n = 15)	Number of patients: - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 29 - Began treatment: 29 - Completed treatment: 27 - Withdrawals/losses to followup: 2 withdrawals Age: Mean (SD): 45 (13)	**1) Blood pressure:** Mean seated BP (SD): (table) P < 0.01 for losartan SBP and DBP pre-	**General comments:** - One patient in the losartan group was excluded from analysis due to ineffective BP control Quality assessment: Overall rating: Poor Comments: - Ill-defined protocol - Not blinded

	Losart Pre-	Losart 120 days	Enal Pre-	Enal 120 days
SBP	153 (18)	138 (16)	141 (14)	134 (10)
DBP	100 (13)	88 (8)	96 (13)	87 (10)

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Enalapril 2.5-10 mg daily (n = 14) Dose titration/co-interventions: Both drugs titrated at discretion of treating MD/investigator Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: NR Baseline/run-in period: 14-day washout of previous antihypertensive meds; no other run-in Duration of treatment: 120 days Duration of post-treatment followup: NA	Median: NR Range: NR **Sex (n [%]):** Female: 14 (48%) Male: 15 (52%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Seated BP measured using a standard mercury sphygmomano-meter; median of 3 readings Losartan / Enalapril SBP 153 ± 18 / 141 ± 14 DBP 100 ± 13 / 96 ± 13 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: - Hypertension - Renal parenchymal disease - Stable renal function Exclusion criteria: - Patients on diuretics at baseline - Require > 1 med for BP control at baseline	/post- P < 0.01 for enalapril DBP pre-/post- (not SBP) **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Generally not reported. 1 patient withdrew from enalapril arm due to cough. No other AEs reported. **6) Specific adverse events:** NR except AEs leading to withdrawal (see immediately above) **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** Mean creatinine clearance (mL/sec 1.73 m^2): Losartan / Enalapril Baseline 1.88 (0.32) / 1.82 (0.21) 120 days 1.90 (0.32)	- Missing information - Large BP differences in treatment groups at baseline (suggesting failure of randomization) **Applicability:** - Source of participants and recruitment not described - No information on AEs - All patients had renal parenchymal disease

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			1.69 (0.21) Mean plasma creatinine (mmol/L): Losartan Enalapril Baseline 0.11 (0.05) 0.11 (0.04) 120 days 0.11 (0.06) 0.11 (0.05) **13) Proteinuria:** NR	
Shibasaki, Masaki, Nishiue, et al., 2002 **#1622**	Geographical location: Osaka, Japan Study dates: Nov 1998 – April 2000 Funding source: Ministry of Education, Science, Sports, and Culture - Japan Interventions: Number of patients randomized to each treatment group NR - Losartan 50 mg daily (n = 10 completed) - Amlodipine 5 mg daily (n = 10 completed) - Enalapril 5 mg daily (n = 10 completed) No dose titration or co-interventions Study design: RCT, parallel-group Blinding:	Number of patients: - Screened for inclusion: 45 - Eligible for inclusion: 38 - Randomized: 38 - Began treatment: 38 - Completed treatment: 30 - Withdrawals/losses to followup: 8 Age: Mean (SD): 55 (3) Median: NR Range: 21-80 **Sex (n [%]):** Female: 11 (37%) Male: 19 (63%) Race/ethnicity (n [%]): NR - presume all native Japanese **Baseline blood pressure:** Supine pre-dialysis (only mean BP reported); measured using mercury sphygmomanometer	**1) Blood pressure:** Mean BP, supine and pre-dialysis (seated values, supine SBP and DBP not reported); number analyzed is 10 per group: | | Losartan | Enalapril | Amlodi-pine | |---|---|---|---| | Baseline | 101.5 (4) | 101.2 (3.3) | 99.3 (2.2) | | 6 mo | 90.8 (2.5) | 90.1 (0.9) | 88.3 (1.7) | P < 0.05 for all pre-post differences. No p-values reported for between-group differences. **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** 1 death (treatment group not specified) **4) Morbidity:** 1 MI (treatment group not specified) **5) Safety:**	**General comments:** See below Quality assessment: Overall rating: Fair Comments: - Small study - Single center - Number of patients randomized to various treatment groups NR - See comments immediately below, under Applicability **Applicability:** - Probably does not reflect equivalent doses of enalapril and losartan, biasing results in favor or losartan - Reports only mean arterial pressure (not SBP, DBP), so difficult to compare to other studies - Unique dialysis population; may not generalize to non-dialysis hypertensive patients

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Patients: Yes - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: NR Baseline/run-in period: 2 wk (intervention not described) Duration of treatment: 6 mo Duration of post-treatment followup: NA	Baseline mean BP (SD) reported for n = 30 completers: Losartan: 101.5 (4) Enalapril: 101.2 (3.3) Amlodipine: 99.3 (2.2) **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** Diabetes: Total - 12/30 (40%) Each group had 4/10 (40%) **Recruitment setting:** Single dialysis center in Osaka, Japan Inclusion criteria: - Uremia referred for dialysis - On maintenance dialysis for at least 1 mo - Maintained stable post-dialysis weight - SBP > 150 or DBP > 90 Exclusion criteria: - History of ischemic heart disease - History of CVA - Inadequate echocardiogram for LV mass - Atrial fibrillation - Recurrent CHF - Significant valvular heart disease - Nephritic syndrome - History of neoplasia	7 patients withdrawn from study and not included in analysis: - 1 had heart attack - 1 switched from hemo to peritoneal dialysis - 1 had myocarditis - 1 had death from pulmonary bleeding - 3 transferred to other hospitals No information on initial treatment arm for above withdrawals **6) Specific adverse events:** NR except AEs leading to withdrawal (see immediately above) **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** Mean (SD) Left Ventricular Mass Index (g/m^2): Losartan / Enalapril / Amlodipine Baseline: 154.5 (9.9) / 155.6 (14.3) / 156.6 (7.3) 6 mo: 114.6 (5.8) / 135.3 (10.4) / 137.2 (4.1) Change: -24.7 (3.2) / -11.2 (4.1) / -10.5 (5.2) P < 0.05 for all pre-post for losart and enalapril, but not amlodipine P< 0.05 for difference in losartan group	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td></td><td></td><td>compared to enalapril or amlodipine

They also report measurements of interventricular septum, posterior wall, end-diastolic volume index, collapsibility index of IVC and LV ejection fraction

12) Creatinine/GFR:
Mean (SD) serum Cr (mg/mL):
<table><tr><td></td><td>Losartan</td><td>Enalapril</td><td>Amlodi-pine</td></tr><tr><td>Baseline</td><td>9.0 (0.4)</td><td>9.9 (0.7)</td><td>8.7 (0.5)</td></tr><tr><td>6 mo</td><td>9.2 (0.5)</td><td>10.2 (0.5)</td><td>9.4 (0.9)</td></tr></table>
13) Proteinuria: NR</td><td></td></tr>
<tr><td>Simons, Ortiz, and Calcino, 2008

#132</td><td>Geographical location: Australia

Study dates: Jan 2004 – Dec 2006

Funding source: Project was commissioned by Solvay Pharmaceuticals Australia

Interventions: Analysis of patients prescribed antihypertensive medications, mostly (86%) by general practitioners. Analysis restricted to patients using ARBs, ACEIs, or calcium-channel blockers, including products combined with a diuretic.

Were additional anti-hypertension medications allowed: Yes</td><td>Number of patients: N = 48,690
- Screened for inclusion: NR
- Eligible for inclusion: 48,690
- Randomized: NA
- Began treatment: NA
- Completed treatment: NA
- Withdrawals/losses to followup: NA

Age:
Range:
< 50: 6330 (13%)
50-69: 18,502 (38%)
≥ 70: 23,858 (49%)

Sex (n [%]):
Female: 27,266 (56%)
Male: 21,424 (44%)

Race/ethnicity (n [%]): NR

Baseline blood pressure: NR</td><td>1) Blood pressure: NR

2) Rate of use of a single antihypertensive agent for BP control: NR

3) Mortality: NR

4) Morbidity: NR

5) Safety: NR

6) Specific adverse events: NR

7) Persistence/adherence:
<u>Cessation</u> defined as no prescription refills for at least 3 calendar months.

<u>Persistence</u> defined as remaining on therapy (i.e., no cessation). “No major differences in persistence patterns between patients taking A2RAs [ARBs] and ACEIs.”</td><td>General comments:
Assessed only persistence and a surrogate for adherence

Quality assessment:
Overall rating: Fair

Comments:
Aggregate data and retrospective study, but sample is probably representative of study population

Applicability:
Limited to a subset of Australian Medicare patients</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	If Yes to above, was this done: At discretion of clinician/investigator Study design: Other – retrospective analysis of 10% random sample for AHT drugs Blinding: - Patients: No - Providers: No - Assessors of outcomes: NA Was allocation concealment adequate?: NA Baseline/run-in period: NA Duration of treatment: 2-year period of data collection Duration of post-treatment followup: NA	**Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** All Australian long-term health concession card holders, for whom all prescriptions are recorded. Analysis restricted to patients using ARBs, ACEIs, or calcium-channel blockers, including products combined with a diuretic. Inclusion criteria: Analysis was performed on a cohort of patients who had been prescribed one of the eligible drugs during the period 1/2004 to 9/2006, but for whom no prescription for any antihypertensive medication had been filled during the previous 6 months. Exclusion criteria: See above.	"Within the A2RA [ARB] class, patients commencing on candesartan or telmisartan showed the best apparent persistence (by a margin of 10%-20%); within the ACEI class, patients prescribed perindopril showed the best apparent persistence (about 25% better than other class members)." A medication possession ratio (MPR) was calculated for patients persisting with treatment as a surrogate for adherence. "Median MPRs were close to 100%, with the notable exception of captopril (72%)." Detailed data provided in Tables 1-4 of article. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Solomon, Appelbaum, Manning, et al., 2009 **#69** ALLAY	Geographical location: 77 centers in 8 countries (specific locations NR) Study dates: NR Funding source: Novartis Pharmaceuticals Corp., East Hanover, NJ	Number of patients: N = 460 - Screened for inclusion: 1104 - Eligible for inclusion: 465 - Randomized: 465 - Began treatment: 465 - Completed treatment: 400/465 (86%) - Withdrawals/losses to followup: 65/465 (14%)	**1) Blood pressure:** Only patients who were treated for at least 28 weeks and had both CMR measures were included in the efficacy population (aliskiren n = 133; losartan n = 129; combo n = 138; these n's refer to outcomes #2 & 11 below; full sample used for #1, 5, 6) BP reduction, mm Hg (SD):	**General comments:** Results of combination treatment not included in this table Quality assessment: Overall rating: Good Comments: Unclear why some assessments

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
(Aliskiren in Left-Ventricaular Hypertrophy) study	"The study was designed jointly by the academic steering committee and the sponsor. The sponsor was involved in the study management, data collection, and data analysis." Interventions: 1) Aliskiren 150 mg/d, increased to 300 mg/d after 2 weeks (n = 154) 2) Losartan 50 mg/d, increased to 100 mg/d after 2 weeks (n = 152) 3) Aliskiren plus losartan, same dosage and titration as above (n = 154) Were additional anti-hypertension medications allowed: Yes If Yes to above, was this done: Per protocol. Could add diuretics during first week. Additional non-RAAS inhibitor or non-beta-blockers could be added during course of the study to reach BP goal < 140/90 for nondiabetics or < 130/80 for diabetics. Study design: RCT, parallel-group. Randomization stratified according to ACEI/ARB use or not prior to study. Blinding: - Patients: Yes	Of the 465 randomized, 5 were excluded from analysis because of data quality concerns. Age: Mean (SD): 58.8 ±10.4 **Sex (n [%]):** Female: 112 (24.3%) Male: 348 (75.7%) Race/ethnicity (n [%]): White: 433 (94.1%) Other: 27 (5.9%) **Baseline blood pressure:** Assessed at each visit with a calibrated standard sphygmomanometer. Mean of 3 measurements while sitting. <u>Aliskiren:</u> SBP, mm Hg (SD): 145.7 (14.1) DBP, mm Hg (SD): 89.2 (9.6) <u>Losartan:</u> SBP, mm Hg (SD): 146.1 (13.4) DBP, mm Hg (SD): 89.0 (10.0) **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** <u>Aliskiren Losartan</u> History of diabetes 35(22.7) 34(22.4) Current smoker 33(21.4) 29(19.1)	Aliskiren: SBP: 6.5 (14.9) DBP: 3.8 (10.1) Losartan: SBP: 5.5 (15.6) DBP: 3.7 (10.7) Figure 3 in paper reports BP changes at multiple time points. **2) Rate of use of a single antihypertensive agent for BP control:** Aliskiren: 45/133 (34%) Losartan: 45/129 (35%) See Table 5 in paper for further details. **3) Mortality:** No deaths **4) Morbidity:** NR **5) Safety:** Any AE (n [%]): Aliskiren: 91/154 (59%) Losartan: 82/152 (54%) Serious AEs (n [%]): Aliskiren: 10/154 (6.5%) Losartan: 13/152 (9%) Discontinuations due to AEs (n [%]): Aliskiren: 4/154 (3%) Losartan: 10/152 (7%) **6) Specific adverse events:** Most common AEs (> 5%): <u>Aliskiren Losartan</u> Headache 14 (9%)	(like those for outcome 2, at left) were reported in subcohort that underwent cMRI **Applicability:** Good applicability for head-to-head comparison of aliskiren and losartan

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Providers: Yes - Assessors of outcomes: Yes Double-dummy design. Was allocation concealment adequate?: Yes Baseline/run-in period: 2 weeks for patients not on an ACEI or ARB at time of enrollment; 3 months for patients on an ACEI or ARB, during which time they discontinued the ACEI or ARB (non-RAAS blocking agents could be prescribed to control BP during this period) Duration of treatment: 2 weeks of titration, plus 34 weeks of maintenance Duration of post-treatment followup: None (last assessment 34 weeks after start of treatment)	**Recruitment setting:** NR Inclusion criteria: - History of or newly diagnosed HTN with SBP/DBP ≥ 140/90 mmHg but < 180/110 mmHg - Confirmed LV wall thickness in any wall by a screening echocardiogram of ≥ 13 mm - BMI > 25 kg/m^2 Exclusion criteria: - LVEF < 40% - Required continued treatment with an ACEI or ARB - Patients treated at entry with an ACEI or ARB who did not complete the 3-month washout period - Severe BP elevation - Serum creatinine > 1.7 mg/dL at visit 1 - Severe obesity (BMI ≥ 42 kg/m^2) - Patients with pacemakers, implantable cardioverter-defibrillators, or defibrillators - History of MI, coronary artery bypass surgery, percutaneous coronary intervention, transient ischemic attack, or stroke within 6 months of study entry\.	8 (5%) Nasopharyngitis 11 (7%) 13 (9%) Diarrhea 6 (4%) 9 (6%) No statistically significant differences between groups. **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** LV mass assessed via cardiovascular magnetic resonance (CMR), pre-post intervention. "Highly significant reductions in LVMI from baseline in all treatment groups." See Table 3 and Figure 4 in paper for details. **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Sonoda, Aoyagi, Takenaka, et al., 2008 **#120**	Geographical location: Japan Study dates: NR Funding source: NR Interventions:	Number of patients: N = 50 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: 50 - Completed treatment: 50 - Withdrawals/losses to followup:	**1) Blood pressure:** Losartan, mm Hg (SD): SBP: 127 (19) DBP: 75 (10) Mean: 92 (11) Enalapril or imidapil, mm Hg (SD):	**General comments:** Significant potential bias due to poor study design and inadequate reporting Quality assessment: Overall rating: Poor

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Nonrandomized allocation to: - Losartan 50 mg/d (n = 22); - Enapril or imidapril 5 mg/d (n = 14; of these, 11 received enalapril and 3 received imidapril); 0 Control (no ACEI or ARB; n = 14) Were additional anti-hypertension medications allowed: Yes If Yes to above, was this done: NR Study design: Nonrandomized, 3-arm, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: NR Was allocation concealment adequate?: NA Baseline/run-in period: NR Duration of treatment: 12 months Duration of post-treatment followup: None (last assessment after 12 months of treatment)	0 ("none of the patients dropped out of the study") Age: Mean (SD): 64.1 ± 9.3 **Sex (n [%]):** NR Race/ethnicity (n [%]): NR **Baseline blood pressure:** Assessment method for BP not reported Losartan, mm Hg (SD): SBP: 138 (25) DBP: 82 (12) Mean: 101 (14) Enalapril or Imidapil, mm Hg (SD): SBP: 127 (26) DBP: 67 (11) Mean: 92 (11) **Concurrent non-hypertension medications (n [%]):** Losartan Enal/imidapril Aspirin 9/22 (41%) 7/14 (50%) Statins 6/22 (27%) 3/14 (21%) β-blocker 6/22 (27%) 3/14 (21%) **Comorbidities (n [%]):** Losartan Enal/imidapril Diabetes 5/22 (23%) 1/14 (7%)	SBP: 125 (24) DBP: 71 (14)) Mean: 89 (16) **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** Cholesterol, mg/dL (SD): Losartan Baseline: 202.1 (23.5) Followup: 188.8 (24.1) Enalapril or Imidapil Baseline: 192.7 (21.7) Followup: 200.2 (19.2) Triglycerides, mg/dL (SD): Losartan Baseline: 199.5 (137.0) Followup: 205.0 (126.0) Enalapril or imidapil Baseline: 106.0 (58.5) Followup: 156.0 (128.0) Followup results were not statistically significant between groups	Comments: -Non randomized - Open-label - Small sample size - 2 different ACEIs in ACEI arm - Many baseline differences between study arms - Inadequate reporting of patient population, methods, and results (no BP results) **Applicability:** Inadequate reporting of study populations, methods, interventions, and results

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Uncontrolled diabetes 3/22 (14%) 1/14 (7%) **Recruitment setting:** NR Inclusion criteria: Systemic HTN Exclusion criteria: Patients on hemodialysis or with renal failure	**9) Progression to type 2 diabetes:** Prevalence of "diabetes mellitus" at baseline and 12-mo followup: <u>Losartan</u> Baseline: 5/22 (23%) Fu: 5/22 (23%) <u>Enalapril or Imidapril</u> Baseline: 1/14 (7%) Followup: 1/14 (7%) Prevalence of "uncontrollable diabetes mellitus" at baseline and 12-mo followup: <u>Losartan</u> Baseline: 2/22 (9%) Followup: 3/22 (14%) <u>Enalapril or Imidapril</u> Baseline: 1/14 (7%) Followup: 1/14 (7%) **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR **14) Other:** Intima-media thickness change from baseline: Losartan: -0.076 ± 0.118; Enalapril or imidapril: -0.073 ± 0.109 No difference between those 2 arms, but significant decline compared to baseline in	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			both arms	
Souza-Barbosa, Ferreira-Melo, Ubaid-Girioli, et al., 2006 **#234**	Geographical location: Campinas, SP, Brazil Study dates: NR Funding source: Fundação de Amparo à Pesquisa do Estado de São Paulo Interventions: Five groups: 1) Normotensive controls (n = 25); 2) HCTZ 25-50 mg/d (n = 18); 3) Quinapril 20 mg/d (n = 16); 4) Irbesartan 150 mg/d (n = 14); 5) Quinapril 20 mg/d plus irbesartan 150 mg/d (n = 25) Controls administered neither drugs nor placebo Were additional anti-hypertension medications allowed: NR Study design: RCT, parallel-group. 5 arms total: 1 arm comprised of normal controls, 4 arms comprised of patients with hypertension randomized to a drug regimen Blinding: - Patients: No - Providers: No - Assessors of outcomes: Yes	Number of patients: N = 88 (25 normotensives and 63 hypertensives) - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NR - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR Note: sample sizes were provided for each intervention group, but it is not clear whether those sample sizes were for patients who started treatment, completed the 12-month study, or both Age: Mean (SD): 49 ±7.6 **Sex (n [%]):** Female: 51 (58.0%) Male: 37 (42.0%) Race/ethnicity (n [%]): Black: 49 (55.7%) Other: (44.3%) **Baseline blood pressure:** Mean 24-hour SBP, using ambulatory blood pressure monitoring (Spacelabs). <u>Quinapril</u> SBP, ABPM, mm Hg (SD): 150 (14)	**1) Blood pressure:** <u>Quinapril</u> SBP, ABPM, mm Hg (SD): 117 (16) DBP, ABPM, mm Hg (SD): 76 (10) <u>Irbesartan</u> SBP, ABPM, mm Hg (SD): 136 (8) DBP, ABPM, mm Hg (SD): 71 (10) **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	**General comments:** - Results for other 3 study arms not included here - Study also includes data on flow-mediated dilation to assess endothelial function Quality assessment: Overall rating: Poor Comments: Inadequate reporting of methods, recruitment, treatment, and followup **Applicability:** - Baseline differences in BP between groups - Inadequate reporting of methods, recruitment, treatment, followup - No information about cointerventions

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Was allocation concealment adequate?: NR Baseline/run-in period: None Duration of treatment: 12 weeks Duration of post-treatment followup: None (last measurement 12 weeks after start of treatment).	DBP, ABPM, mm Hg (SD): 94 (11) <u>Irbesartan</u> SBP, ABPM, mm Hg (SD): 168 (15) DBP, ABPM, mm Hg (SD): 90 (12) **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** Hypertensive subjects recruited from patients diagnosed in the outpatient hypertension clinic at a university hospital Inclusion criteria: Diagnosis of hypertension in outpatient hypertension clinic Exclusion criteria: - Secondary forms of HTN - Pheochromocytoma - Renal artery stenosis - Primary hyperaldosteronism - Aortic coarctation - Impaired renal function - Ischemic heart disease, liver diseases, and other major disease - Recent use of medicines that affected vascular function, including statins, prostaglandin inhibitors, vitamins, contraceptives (within the previous 2 months), and		

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		acetylsalicylic acid (within the previous 7 days) - Dyslipidemia, DM, or evidence of hepatic, renal, or hematologic dysfunction		
Spinar, Vitovec, Soucek, et al., 2009 **#36**	Geographical location: Czech Republic Study dates: Jan 06 – Dec 07 Funding source: The Ministry of Education of the Czech Republic (0021 622 402) Interventions: Group A (CORD 1A): 4016 patients previously on an ACEI for > 3 months were switched to losartan 50 mg/day. Dose could be lowered to 25 mg at clinician's discretion. If BP ≥ 140/90 at 1 or more months, dose increased to 100 mg. If BP ≥ 140/90 after ≥ 3 months of treatment, another hypertensive drug added (usually a thiazide diuretic). Group B (CORD 1B): 3813 patients with stable BP ≥ 140/90 for at least 3 months prior, and not currently treated with an ACEI or ARB. Ramipril (recommended 5 mg, but could be 2.5 mg) vs. losartan (recommended 50 mg, but could be 25 mg). Dose increased at ≥ 1 month if BP ≥ 140/90. If BP ≥ 140/90 after ≥ 3 months of treatment of ramipril 10 mg or	Number of patients: N = 7829 with 6-month followup data, but no clear reporting of the number of patients enrolled <u>CORD 1A:</u> - Screened for inclusion: 11,284 - Eligible for inclusion: NR - Randomized: NA - Began treatment: Ambiguous and possibly erroneous reporting. The abstract reported that 4016 patients were enrolled, but this is also the number of patients that completed the 6-month assessment. - Completed treatment: 4016 at 6 months, and 3022 at 12 months - Withdrawals/losses to followup: NR. By inference, based on ambiguous data reporting in Figure 1 and Table 1, there were no withdrawals, death, or losses to followup in either CORD 1A or CORD 1B at the 6-month followup, except for 72 patients withdrawn because of adverse events. Which group these 72 patients were originally allocated to is not reported. If 72 is the total number of patients who withdrew or were lost to followup, the retention rate at 6 months for CORD 1A and 1B combined	**1) Blood pressure:** Blood pressure at 12 months (SBP/DBP, mmHg, mean [± SD]): CORD 1A: 133.6 ± 10.3 / 79.0 ± 6.5 CORD 1B: - Ramipril: 134.1 ± 11.2 / 79.3 ± 6.9 - Losartan: 134.5 ± 11.3 / 80.1 ± 6.6 No statistically significant differences between groups Percentage of patients moving from hypertension to normotension at 6 months: CORD 1A: 31.7% CORD 1B: - Ramipril: 45.6% - Losartan: 46.6% **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** CORD 1A: 6 deaths (0.1%) CORD 1B: 4 deaths in ramipril group (0.2%) and 5 deaths in losartan group (0.2%) **4) Morbidity:** CORD 1A: - MI: 7/4016 (0.2%) - Stroke: 14/4016 (0.3%) - New diabetes mellitus: 9/4016 (0.2%) CORD 1B: <u>Ramipril</u> <u>Losartan</u> - MI: 4 (0.2%) 3 (0.2%)	**General comments:** Unable to assess for potentially significant bias because of inadequate and ambiguous reporting Quality assessment: Overall rating: Poor Comments: Inadequate reporting of study design, methods, and results. It appears that patients who enrolled and/or started treatment but did not complete the 6-month assessment were excluded from all analyses, including baseline analyses. Study design, however, is innovative, with potentially informative findings had they been reported in a way that would have allowed unambiguous interpretation. **Applicability:** - Selection and withdrawal of participants poorly reported - Indirect comparison in CORD 1A

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	losartan 100 mg, another hypertensive drug added (usually a thiazide diuretic). Were additional anti-hypertension medications allowed: Yes, both prior to enrollment, and as additional treatment during study period If Yes to above, was this done: At discretion of clinician/investigator, within parameters specified per protocol Study design: CORD 1A: Prospective cohort, with pre-intervention comparison C0RD 1B: RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: NR Was allocation concealment adequate?: No Baseline/run-in period: NA Duration of treatment: 12 months Duration of post-treatment followup: None. Followup upon completion of 12-month treatment period	would be 7757/7829 = 99%. The corresponding 12-mo retention rate (assuming 7829 were enrolled) is 5832/7829 = 75%. <u>CORD 1B:</u> - Screened for inclusion: 11,284 - Eligible for inclusion: NR - Randomized: Ambiguous and possibly erroneous reporting. The abstract reported that 3813 patients were enrolled (1926 in ramipril group and 1887 in losartan group), but this is also the number of patients that completed the 6-month assessment. - Began treatment: See above. It appears that data are reported only for patients who completed the 6-month followup. - Completed treatment: Ramipril: 1926 at 6 months and 1416 at 12 months. Losartan: 1887 at 6 months and 1394 at 12 months - Withdrawals/losses to followup: NR relative to start of treatment, but 510/1926 (26%) and 493/1887 (26%) lost to followup or withdrawn between months 6 and 12 for ramipril and losartan, respectively, not counting the 72 patients in CORD 1A and 1B reported to have been withdrawn because of side effects. Age: CORD 1A: Mean (SD): 62.6 ± 11.6 CORD 1B:	- Stroke 8 (0.4%) 9 (0.5%) - New diabetes: 6 (0.3%) 5 (0.3%) **5) Safety:** See Morbidity above. **6) Specific adverse events:** Incidence of cough, n (%) <u>CORD 1A</u> <u>Ramipril</u> <u>Losartan</u> 3 (< 0.1%) 33 (2%) 4 (0.2%) **7) Persistence/adherence:** NR **8) Lipid levels:** Cholesterol, mmol/L: <u>Baseline</u> <u>Month 12</u> CORD 1A 5.44.4 ± 0.4 5.2 ± 0.8 CORD 1B - Ramipril 5.4 ± 1.0 5.2 ± 0.8 - Losartan 5.5 ± 1.0 5.3 ± 0.9 Triglycerides, mmol/L: <u>Baseline</u> <u>Month 12</u> CORD 1A 1.9 ± 0.9 1.8 ± 0.8 CORD 1B - Ramipril 1.9 ± 0.9 1.8 ± 0.7 - Losartan 1.9 ± 0.9 1.8 ± 0.7 Within-group changes from baseline and between-groups comparisons of these changes were not statistically significant **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** Glycemia, mmol/L: <u>Baseline</u> <u>Month 12</u> CORD 1A 5.9 <u>+</u> 1.6 5.7 <u>+</u> 1.4	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Ramipril: Mean (SD): 60.4 ± 12.5 - Losartan: Mean (SD): 60.6 ± 11.8 **Sex (n [%]):** CORD 1A: Female: 53.1% (calculated n = 2132) CORD 1B: - Ramipril: Female: 49.0% (calculated n = 944) - Losartan: Female: 52.1% (calculated n=983) Race/ethnicity (n [%]): NR **Baseline blood pressure:** <u>CORD 1A</u> SPB: 147.4 (SD 14.8) mm Hg DBP: 87.7 (SD9.3) mm Hg <u>CORD 1B, ramipril</u> SBP: 155.9 (SD 13.1) DBP: 134.9 (SD 10.5) <u>CORD 1B, losartan</u> SBP: 156.5 (SD 13.1) DBP: 93.4 (SD 8.8) **Concurrent non-hypertension medications (n [%]):** CORD 1A: Aspirin: 36% Warfarin: 4% Statin: 44% Nitrate: 15% Oral antidiabetic med: 15% CORD 1B:	CORD 1B - Ramipril 5.9 ± 1.8 5.7 ± 1.3 - Losartan 5.8 ± 1.6 5.7 ± 1.5 **11) LV mass/function:** NR **12) Creatinine/GFR:** Creatinine, micromol/L: <u>Baseline Month 12</u> CORD 1A 91.5 ± 20.7 91.6 ± 19.5 CORD 1B - Ramipril 89.5 ± 18.5 90.2 ± 18.4 - Losartan 91.1 ± 20.1 91.2 ± 20.2 **13) Proteinuria:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Aspirin: 31% Warfarin: 3% Statin: 38% Nitrate: 12% Oral antidiabetic med: 12% **Comorbidities (n [%]):** CORD 1A: Diabetes mellitus: 33% Previous MI: 13% Dyslipidemia: 61% CORD 1B: Diabetes mellitus: 29% Previous MI: 12% Dyslipidemia: 55% **Recruitment setting:** Patients of 585 doctors in the Czech Republic Inclusion criteria: - Treated with an ACEI for > 3 months - BP < 160/100 mmHg - Treatment with additional antihypertensive agents, other than an ARB, was allowed Exclusion criteria: Any documented cardiovascular event during the 3 months prior to screening		
Spoelstra-de Man, van Ittersum, Schram, et al., 2006	Geographical location: A University Medical Center in Amsterdam & 5 other hospitals in the same region Study dates: July 1998 – Oct	Number of patients: N = 70 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 70 - Began treatment: - Completed treatment:	**1) Blood pressure:** Sitting BP: - Candesartan: 67% achieved BP goals after the titration phase, with the median use of 3 antihypertensive drugs - Lisinopril: 68% achieved BP goals after	**General comments:** - Study initially powered to detect a significant change in LVMI, but recruitment ended before enrolling the anticipated 38 patients/group - Enrolled only patients with DM

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	2001	- Withdrawals/losses to followup: 10 (1 lost to followup; 9 discontinued intervention)	the titration phase, with the median use of 3 antihypertensive drugs	and HTN
#260	Funding source: AstraZeneca provided funding but had no influence on the data analyses or manuscript preparation	Age: Mean (SD): 61.7 (7) Range: 35-70	Mean BP at 12 months, mm Hg (SD) Candesartan Lisinopril SBP: 128 (13) 126 (15) 76 (9) 73 (7)	Quality assessment: Overall rating: Good Comments: - Adequate blinding - Head-to-head comparison of antihypertensive therapy strategies with either candesartan or lisinopril as initial therapy
	Interventions: Patients randomized to: - HCTZ 12.5 mg (n = 24) - Candesartan 8 mg (n = 24) - Lisinopril 10 mg (n = 22)	**Sex (n [%]):** Female: 27 (38.6%) Male: 43 (61.4%)	**2) Rate of use of a single antihypertensive agent for BP control:** NR	**Applicability:** - Complicated drug titration protocol
	Titration period of 4-6 months after randomization to achieve target BP of 130/85, or a sitting BP decrease of more than 10% combined with a DBP < 85	Race/ethnicity (n [%]): Caucasian: 70 (100%) **Baseline blood pressure:** Ambulatory blood pressure monitoring with a Spacelabs 90207 monitor	**3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR	- Little information about patient population - Extensive exclusion criteria
	Were additional anti-hypertension medications allowed: Yes If Yes to above, was this done: Stepwise titration of dosage and addition of other medications per protocol. HCTZ was co-administered in all groups.	Mean 24h SBP, mm Hg (SD): Candesartan Lisinopril 136 (12) 136 (13) Mean 24h DBP, mm Hg (SD): Candesartan Lisinopril 79 (8) 81 (9)	**6) Specific adverse events:** NR **7) Persistence/adherence:** Complete followup: - Candesartan: 20/24 (83%) - Lisinopril: 21/22 (95%) **8) Lipid levels:** NR	
	Study design: RCT, parallel-group, double blind Randomization occurred after run-in period	Office SBP, mm Hg (SD): Candesartan Lisinopril 151 (14) 149 (9) Office DBP, mm Hg (SD): Candesartan Lisinopril 94 (10) 93 (7)	**9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** LVM decreased by 4% at 6 months and 10% at 12 months in both groups.	
	Blinding: - Patients: Yes at randomization, but not for stepwise increase in dosage or addition of new drugs. - Providers: Yes at randomization, but not for	**Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR	**12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	stepwise increase in dosage or addition of new drugs. - Assessors of outcomes: Yes Double-dummy design, with 2 placebo pills taken per day in addition to active drug. Unblinded protocol for additional therapy as needed. Was allocation concealment adequate?: NR Baseline/run-in period: 1 month Duration of treatment: 12-month treatment period after titration period, beginning with either achievement of target BP, or after completion of 6-month titration period Duration of post-treatment followup: None. Last followup 12 months after beginning of treatment period (which is also the end of the titration period)	**Recruitment setting:** Outpatient clinic in a medical center and 5 other hospitals Inclusion criteria: - Type 2 DM for ≥ 6 months - Age 35-70 - Caucasian ethnicity - Urinary albumin excretion < 100 mg/24 hours Exclusion criteria: - Pregnant or planning pregnancy - History of MI, angina pectoris, coronary artery bypass surgery, angioplasty, stroke, congestive heart failure, malignancy or other serious illnesses - Serum creatinine > 140 μmol - Use of antihypertensive medication in the previous month or ACEIs in the previous 3 months - BMI > 35 kg/m^2 - Alcohol and/or drug abuse - Participation in other clinical trials		

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Tedesco, Natale, and Calabro, 2006 **#249**	Geographical location: Naples, Italy Study dates: NR Funding source: NR Interventions: - Carvedilol 25 mg - Amlodipine 10 mg - Enalapril 20 mg - Losartan 50 mg After 2 months, nonresponders received a low-dose thiazide diuretic, and after 4 months either amlodipine (enalapril, carvedilol, losartan groups) or carvedilol (amlodine group) Discontinuation of treatment and withdrawal from study occurred when SBP did not decrease by 5 or more mm Hg or when the medication was "not tolerated" Were additional anti-hypertension medications allowed: Yes If Yes to above, was this done: Per protocol (see above) Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No	Number of patients: N = 560 - Screened for inclusion: 560 - Eligible for inclusion: 520 (40 excluded due to white coat HTN) - Randomized: 520 - Began treatment: NR - Completed treatment: 466 - Withdrawals/losses to followup: Total: 54 (10%) - Withdrawn 2ary to AE's: 25 (5%) - No BP control: 15 (3%) - Lost to followup: 14 (3%) Age: Mean (SD): 54 (10.5) Range: 29-90 Age reported only for the 466 patients who completed the study **Sex (n [%]):** Female: 186/466 (40.0%) Male: 280/466 (60.0%) Sex distribution reported only for the 466 patients who completed the study Race/ethnicity (n [%]): Caucasian: 560 (100%) **Baseline blood pressure:** By mercury sphygmomanometer on nondominant arm in the early morning, sitting, by a trained investigator, at clinic visits. Mean of 3 readings 10 minutes apart, recorded to the nearest 2 mm.	**1) Blood pressure:** Response to treatment defined as mean sitting BP < 140/90 or a decrease of 10/10 mm Hg in BP from baseline No significant differences in outcomes between study arms BP, 24 months (mm Hg): Enalapril Losartan Mean 24h SBP: 132 ± 8 132 ± 8 Change in SBP: -22 -23 Mean 24h DBP: 85 ± 5 85 ± 5 Change in DBP: -13 -13 Responders (%): Enalapril Losartan One drug: 25 23 Two drugs: 49 50 Three drugs: 26 27 24h BP< 130/80 71 72 **2) Rate of use of a single antihypertensive agent for BP control:** 103/466 (22%) were responders on monotherapy **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Withdrawals due to AEs, n (%) Enalapril Losartan 5 (4%) 2 (2%) Not statistically significant **6) Specific adverse events:** Enalapril Losartan	**General comments:** Appropriate study design with moderate quality reporting, appropriate control groups, and relatively large sample size Quality assessment: Overall rating: Good Comments: Reasonably high-quality study, given the limitations of an unblinded clinical trial with moderately good reporting of methods and results **Applicability:** - Generalizability difficult to determine because of insufficient information about the recruitment setting and patient characteristics - Relatively restrictive exclusion criteria - Limited reporting on cointerventions over the course of the 24 months - All Caucasian sample

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: Previously treated patients who did not have BP controlled by current medication suspended therapy for at least 1 week (by inference, prior to randomization) Duration of treatment: 24 months Duration of post-treatment followup: 0 (24-month visit = final visit)	Spacelabs model 90207 monitor used for ABPM. <u>Enalapril</u> <u>Losartan</u> Mean 24h SBP: 154 ± 7 155 ± 8 Mean 24h DBP: 98 ± 6 98 ± 8 **Concurrent non-hypertension medications (n [%]):** NR. "No patient received concomitant medications known to affect BP or interfere with the metabolic parameters." **Comorbidities (n [%]):** NR **Recruitment setting:** Referral from investigators' outpatient clinic Inclusion criteria: Conventional cuff BP readings used for screening of uncomplicated HTN (SBP 155-169 mmHg and DBP 95-109 mmHg) 24-hr ambulatory BP monitoring (ABPM) used to confirm eligibility (average ABPM BP of ≥ 130/80 mm Hg) Exclusion criteria: - "White coat HTN" - Secondary HTN - Renal failure - Diabetes mellitus - Congestive heart failure	Cough: 4 0 Dizziness 1 2 **7) Persistence/adherence:** "Medication compliance was adequate, with more than 90% of pills having been taken in each treatment group." **8) Lipid levels:** Significant reduction in total cholesterol (-10 mg/dL; $p < 0.03$) in the losartan group, and insignificant increase (1 mg/dL) in the enalapril group **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** No significant differences between groups in systolic and diastolic function indexes, LVMI, or diastolic peak velocity ratios (detailed data in Table 3 of paper includes LVMI, LVH, echo parameters) **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td></td><td>- Atrial fibrillation
- Severe valvular heart disease
- Pregnancy or lactation
- Severe obesity
- Ambiguous reporting of whether history of MI or stroke were exclusion criteria</td><td></td><td></td></tr>
<tr><td>Tikkanen, Omvik, and Jensen, 1995

#1623

and

Nielsen, Dollerup, Nielsen, et al., 1997

#1606</td><td>Geographical location: 32 centers in Finland, Denmark, Iceland, and Norway

Study dates: NR

Funding source: NR

Interventions:
- Losartan 50 mg (n = 202)
- Enalapril 20 mg (n = 205)

No dose titration or co-interventions

Study design:
RCT, parallel-group

Blinding:
- Patients: Yes
- Providers: Yes
- Assessors of outcomes: Yes

Was allocation concealment adequate?: NR

Baseline/run-in period: 2-wk placebo run-in

Duration of treatment: 12 wk

Duration of post-treatment</td><td>Number of patients:
- Screened for inclusion: NR
- Eligible for inclusion: NR
- Randomized: 407
- Began treatment: 399
- Completed treatment: 382
- Withdrawals/losses to followup: 25

Age:
Cannot determine mean age; distribution for total sample:
<table><tr><td>Age</td><td>N</td><td>%</td></tr><tr><td>< 35</td><td>19</td><td>4.7</td></tr><tr><td>35-44</td><td>70</td><td>17.2</td></tr><tr><td>45-54</td><td>152</td><td>37.3</td></tr><tr><td>55-64</td><td>110</td><td>27.0</td></tr><tr><td>> 64</td><td>56</td><td>13.8</td></tr></table>
Sex (n [%]):
Female: 151 (37.1%)
Male: 256 (62.9%)

Race/ethnicity (n [%]): 100% white

Baseline blood pressure:
Trough seated BP measured using a standard mercury sphygmomano-meter after 10 min supine rest; average of 3 readings taken at 1-min intervals</td><td>1) Blood pressure:
N = 399 total for “all patients treated” analysis

Mean (SD) seated trough SBP:
<table><tr><td></td><td>Losartan (n = 200)</td><td>Enalapril (n = 199)</td></tr><tr><td>Baseline</td><td>157.5 (17.1)</td><td>158.8 (16.5)</td></tr><tr><td>12 wk</td><td>146.9 (18.3)</td><td>146.0 (16.9)</td></tr><tr><td>Change</td><td>-10.6 (13)</td><td>-12.9 (12.9)</td></tr></table>p < 0.01 for within-group pre-/post- changes
p < 0.05 enalapril vs. losartan

Mean (SD) seated trough DBP:
<table><tr><td></td><td>Losartan (n = 200)</td><td>Enalapril (n = 199)</td></tr><tr><td>Baseline</td><td>103.1 (6.0)</td><td>103.7 (6.1)</td></tr><tr><td>12 wk</td><td>94.7 (9.0)</td><td>93.0 (7.9)</td></tr><tr><td>Change</td><td>-8.4 (7.1)</td><td>-10.6 (7.2)</td></tr></table>p < 0.01 for within-group pre-/post- changes
p < 0.05 enalapril vs. losartan

Also reported is a separate “per protocol” analysis that excluded patients who did not have BP measured at the appropriate trough time

Also reported is the distribution of treatment response (defined as “excellent, good, fair, or poor”). These results also favored enalapril (p < 0.05).</td><td>General comments:
None

Quality assessment:
Overall rating: Fair

Comments:
- No description of recruiting strategy, allocation, or number of screened patients

Applicability:
- Racially homogeneous population (100% white) with very few comorbidities – does not represent general hypertension population
- There were many protocol deviations in the timing of trough BP measurement resulting in a separate analysis (that was likely post-hoc)</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	followup: NA	Losartan / Enalapril SBP 157.5 ±17.1 / 158.8 ± 16.5 DBP 103.1 ± 6.0 / 103.7 ± 6.1 **Concurrent medications (n [%]):** Patients discontinued other antihypertensive meds **Comorbidities (n [%]):** Not listed, but include category of "secondary diagnoses" (not defined) Secondary Diagnoses – "Yes": Losartan: n = 123 (60.9%) Enalapril: n = 126 (61.5%) Total: n = 249 (61.2%) **Recruitment setting:** Outpatient primary care clinics Inclusion criteria: - Age 20-75 - Sitting DBP 95-120 after 2 wk of placebo Exclusion criteria: - Previous therapy of > 2 antihypertensive meds - Secondary hypertension - Renal impairment (Cr >150 μmol/L) - Proteinuria > 1+ on dipstick - CVA, TIA, or HTN encephalopathy in last 1 yr	**2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** **6) Specific adverse events:** Headache, edema, rash/itching mentioned as AEs, but not quantified. **7) Persistence/adherence:** NR **8) Lipid levels:**	

	Losart, n (%)	Enal, n (%)	p-value
Total AEs	65 (32.2%)	93 (45.4%)	< 0.01
Possibly drug-related AEs	23 (11.4%)	52 (25.4%)	< 0.01
Withdrawals due to AEs	6 (3%)	14 (6.8%)	NS
Withdrawals due to drug-related AEs	3 (1.5%)	12 (5.9%)	< 0.05

	Losart	Enal	p-value
Dry cough at 12 wk	1%	12.2%	< 0.01

	Losartan (mean change %)	Enalapril (mean change %)
Cholesterol level	1.8	-0.2

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

- MI or angina pectoris in last 6 months
- Pregnant or nursing women
- Women of child bearing potential
- Current use of NSAIDs or corticosteroids or drugs known to affect BP
- Uncontrolled DM (fasting BS > 11 mmol/L)
- Obesity (arm circumference >41)
- Serum potassium < 3.5 or > 5.5
- Abnormal liver function test (twice upper limit of normal)
- Hgb level < 100g/dL
- "Other clinically important disease that might interfere with participation"
- Previous adverse reaction or lack of treatment response to ACEI

HDL cholesterol	2.1	1.5
Triglycerides	-3.0	2.3

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control:

	Losartan (mean change %)	Enalapril (mean change %)
Glucose level	-0.8	0

11) LV mass/function: NR

12) Creatinine/GFR:

	Losartan (mean change %)	Enalapril (mean change %)
Creatinine level	-0.1	1.7

13) Proteinuria:
Reported for subgroup of patients only (n = 93 Danish and Finnish patients)

Urinary albumin/creatinine ratio (geometric mean x/- antilog SD) in total subgroup:

	Losartan (n = 46)	Enalapril (n = 47)
Baseline	1.14 x/-2.48	0.95 x/-2.45
12 wks	0.81 x/-2.45	0.73 x/-2.0

Differences are significant pre-/post- ($p < 0.05$), but not between treatments.

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td></td><td></td><td>Urinary albumin/creatinine ratio (geometric mean x/- antilog SD) in microalbuminuric patients (n = 23):

<table><tr><td></td><td>Losartan (n = 12)</td><td>Enalapril (n = 11)</td></tr><tr><td>Baseline</td><td>4.16 x/- 1.73</td><td>3.62 x/- 1.69</td></tr><tr><td>12 wks</td><td>1.77 x/- 3.94</td><td>1.52 x/- 2.21</td></tr></table>
Differences are significant pre-/posts (p < 0.05), but not between treatments.</td><td></td></tr>
<tr><td>Townsend, Haggert, Liss, et al., 1995

#1624</td><td>Geographical location: Philadelphia, PA (31 centers)

Study dates: NR

Funding source: NR (one author from Merck)

Interventions:
- Losartan: 50 mg once daily switched after 8 weeks, if necessary, to 50 mg losartan plus 12.5 mg HCTZ (n = 132)
- Enalapril: 5 mg once daily switched after 4 weeks, if necessary, to 10 mg enalapril and then to 10 mg enalapril and plus 25 mg HCTZ after 8 weeks (n = 136)

Titration at each step was required if the SDP remained ≥ 90 mm.

Early entry was possible if mean</td><td>Number of patients:
- Screened for inclusion:
- Eligible for inclusion:
- Randomized: 268
- Began treatment: NR
- Completed treatment: NR
- Withdrawals/losses to followup: 31, 21 due to AEs, 10 due to protocol violations

Age:
Mean (SD): 54.5, 79.5% < 65 yr
Median: NR
Range: NR

Sex (n [%]):
Female: 136 (51%)
Male: 132 (49%)

Race/ethnicity (n [%]):
Black: 65 (25%)
White: 148 (63%)
Hispanic: 26 (10%)
Oriental: 5 (2%)
Native American: 1 (0.5%)</td><td>1) Blood pressure:
At 12 wk, patients in the losartan group had a mean SBP reduction of 10.3 mm Hg vs. 9.8 mm Hg for enalapril (p = 0.31).

68% of patients taking losartan and 60% of patients taking enalapril reached goal BP (sitting DBP < 90 mm Hg or reduction ≥ 10 mm Hg in sitting DBP vs. baseline; p = 0.16).

No other quantitative data reported for overall group results.

Subgroup results:

<table><tr><td></td><td>Losart</td><td>Enal</td><td>p</td></tr><tr><td>Black (n)</td><td>(33)</td><td>(32)</td><td></td></tr><tr><td>Wk 4</td><td>-6.5</td><td>-3.3</td><td>0.02</td></tr><tr><td>Wk 8</td><td>-6.8</td><td>-5.2</td><td>0.06</td></tr><tr><td>Wk 12</td><td>-10.0</td><td>-8.0</td><td>0.02</td></tr><tr><td>Non-black (n)</td><td>(99)</td><td>(104)</td><td></td></tr><tr><td>Wk 4</td><td>-8.4</td><td>-7.0</td><td>0.10</td></tr><tr><td>Wk 8</td><td>-9.6</td><td>-9.2</td><td>0.47</td></tr><tr><td>Wk 12</td><td>-10.4</td><td>-10.4</td><td>0.51</td></tr></table></td><td>General comments:
- Study setting not described (“centers”)

Quality assessment:
Overall rating: Fair

Comments:
- No quantitative data reported for overall group results

Applicability:
- Sites not described</td></tr>
</table>

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

SDBP of 110-115 was evident at baseline and confirmed and confirmed at a repeat visit within 3 days

Patients stratified by SDBP.
Mild hypertension = mean SDBP 95-104
Moderate =105-115 mm

Study medication: Once a day between 6.30-9.30am.
On the morning of clinic visits no medication until bp was measured: all measurements at end of 24-hr dosing interval

Study design:
RCT, parallel-group

Blinding:
- Patients: Yes
- Providers: NR
- Assessors of outcomes: Yes

Each patient got an active and a placebo of the alternative treatment using a double blind double dummy design

Was allocation concealment adequate?: NR

Baseline/run-in period: 4 week placebo run-in (2 placebo tablets each day in the morning, 1 matching losartan and 1 matching enalapril)

Duration of treatment: 12 weeks

Other: 3 (0.5%)

Baseline blood pressure:
At each visit sitting SBP at trough at end of dosing interval and before administration of daily dose. BP measurements after 5 min of rest, in sitting position using a standard mercury sphygmomanometer. Readings repeated to obtain 3 consecutive readings within 1 min interval that did not vary by more than 5 mm from the calculated average of last 3 readings.

Primary endpoint was change in mean sitting DBP from baseline to end of study

Baseline SiDBP:
Losartan: 101 ± 5
Enalapril: 100 ± 4

Concurrent medications (n [%]):
NR

Comorbidities (n [%]): NR

Recruitment setting: NR

Inclusion criteria:
Mean SDBP ≥ 95 and ≤ 115 mm, and did not vary by more than 7 mm between measurements

Exclusion criteria:
- Previously recd. ACE or ARBs
- Sensitivity or intolerance to

≥ 65 yr	(25)	(30)	
Wk 4	-9.0	-6.4	0.06
Wk 8	-9.6	-8.4	0.17
Wk 12	-12.7	-10.1	0.03
< 65 yr	(107)	(68)	
Wk 4	-7.6	-4.9	0.19
Wk 8	-8.7	-8.6	0.06
Wk 12	-9.8	-8.6	0.75

2) Rate of use of a single antihypertensive agent for BP control:
Of 132 losartan patients, 62 (47%) received 5 mg losartan alone, 70 (53%) received 50 mg losartan + 12.5 mg HCTZ by end of study. Of 130 enalapril patients: 33 (24%) received 5 m enalapril, 39(29%) were titrated to and contin taking 10 mg enalapril, and 64(47%) received mg enalapril + 25 mg HCTZ by end of study. Between-group differences were not statistica significant.

3) Mortality: NR

4) Morbidity: NR

5) Safety:
No lab test AEs were serious, no ECG AEs were serious

66% of enalapril patients had 1 or more AE
55% of losartan patients had 1 or more AE

35/132 losartan patients (27%) and 36/136 enalapril patients (26%) had a drug-related AE; no patient had a serious drug-related AE

No statistically significant difference in the number of patients who withdrew due to an AE (9 losartan vs. 12 enalapril)

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		either drug		
	Duration of post-treatment followup: NA	- History of angioedema, heart failure, sec hypertension, malignant hypertension, hypertensive encephalopathy, hypertensive retinopathy, potentially life-threatening arrythmias, decompensated valvular disease, MI, angioplasty, recent coronary bypass surgery, cerebrovascular accident - Pregnant or breast-feeding women	**6) Specific adverse events:** Most common AEs (losartan, enalapril): Headache: 10%, 15% Cough: 7%, 12% URI: 8%, 10% Dizziness: 5%, 7% Asthenia: 6%, 2% Drug-related AEs (losartan, enalapril): Cough: 4%, 10% Headache: 4%, 4% Dizziness: 2%, 3% Asthenia/fatigue: 27%, 26% **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Uchiyama-Tanaka, Mori, Kishimoto, et al., 2005 **#1625**	Geographical location: Osaka, Japan Study dates: NR Funding source: NR Interventions: - Quinapril 10 mg (n = 25) - Losartan 50 mg (n = 18)	Number of patients: - Screened for inclusion: 58 - Eligible for inclusion: NR - Randomized: 57 - Began treatment: 57 - Completed treatment: NR - Withdrawals/losses to followup: NR Age:	**1) Blood pressure:** Quinapril vs. losartan results reported only for patients who achieved response on monotherapy Mean BP (± SD) at 1 yr (monotherapy responders only): Quinapril alone (n = 25) Losartan alone (n = 18)	**General comments:** - Quinapril vs. losartan results reported only for patients who achieved response on monotherapy - Open-label study allowing for bias in assessment Quality assessment: Overall rating: Fair

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Dose titration and co-interventions: If BP not controlled at 2 mo, then given combination of 2 study drugs (i.e., quinapril 10 mg + losartan 50 mg) Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: None Duration of treatment: 1 yr Duration of post-treatment followup: NA	Mean (SD): 61 ± 9 Median: NR Range: NR **Sex (n [%]):** Female: 32 (56%) Male: 25 (44%) Race/ethnicity (n [%]): NR, but presumably 100% Asian **Baseline blood pressure:** Trough seated BP measured 3 times at 2-min intervals with patient resting using an automatic sphygmomanometer; average of 2 "most stable" readings used Baseline values (mean ± SD): Quinapril alone (n = 25): SBP 156 ± 14; DBP 92 ± 9 Losartan alone (n = 18): SBP 156 ± 12; DBP 92 ± 10 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]; n = 43 monotherapy responders):** History of smoking: 17 (39.5%) History of diabetes: 11 (26%) History of hyperlipidemia: (37%) **Recruitment setting:** Outpatients attending renal and	SBP 136 ± 7 / 135 ± 6 DBP 78 ± 7 / 76 ± 8 No significant difference between groups (p-value NR) **2) Rate of use of a single antihypertensive agent for BP control:** 14/57 (25%) took combination quinapril and losartan due to inadequate BP control at 2 mo. Remainder (43/57 = 75%) stayed on monotherapy. **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** Quinapril mono-therapy (n = 25) / Lisinopril mono-therapy (n = 18) LDL baseline: 134 (43) / 121 (27) LDL 1 yr: 126 (27) / 117 (31) HDL baseline: 56 (19) / 49 (13) HDL 1 yr: 59 (20) / 52 (16) TG baseline: 147 (56) / 156 (73) TG 1 yr: 150 (69) / 169 (55)	Comments: - Recruitment and randomization not clearly described - Open-label study allowing for bias in assessment of outcomes - No data on safety/AEs or withdrawals **Applicability:** - Study location in single Japanese medical center - No reporting on safety/AEs/withdrawals - Quinapril vs. losartan results reported only for patients who achieved response on monotherapy

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		hypertension center at the university medical center Inclusion criteria: - Untreated hypertension - Diagnosed at the renal and htn center - Mild-to-moderate essential hypertension accord to Japanese Society of Hypertension guidelines Exclusion criteria: - Signs, symptoms, or history of cardiac or renal disease, cerebrovascular accident, or any major disease - Required anti-platelet or anti-coagulation medications	None of the changes was statistically significant but no p-values reported Note: Patients taking antihyperlipidemia were *not* excluded, so cannot necessarily attribute lipid changes to study drugs **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** Quinapril monotherapy (n = 25); Lisinopril monotherapy (n = 18) HgA1c baseline: 5.5 (1.2); 5.4 (1.1) HgA1c 1 yr: 5.4 (1.0); 5.3 (1.5) None of the changes was statistically significant but no p-values reported Note: Patients taking antidiabetes drugs were *not* excluded **11) LV mass/function:** NR **12) Creatinine/GFR:** Quinapril monotherapy (n = 25); Lisinopril monotherapy (n = 18) Cr baseline: 0.6 (0.2); 0.7 (0.3) Cr 1 yr: 0.7 (0.3); 0.7 (0.2) Cr reported in mg/dL	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			None of the changes was statistically significant but no p-values reported **13) Proteinuria:** NR	
Verdecchia, Schillaci, Reboldi, et al., 2000 **#1626**	Geographical location: Perugia, Italy Study dates: NR Funding source: Supported in part by grants from the associzone umbra cuore e lapertensione, perugia, italy Interventions: - Losartan 50 mg daily (n = 22) - Enalapril 20mg daily (n = 66) Dose titration/cointerventions: In both groups, HCTZ 25 mg daily added if needed (SBP ≥ 140 or DBP > 90) Study design: Case-control selected from observational registry (n = 701) Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: No randomization Baseline/run-in period: NA Duration of treatment: Average of 3.3 yr	Number of patients: - Screened for inclusion: 701 (from cohort) - Eligible for inclusion: NR - Randomized: NA - Began treatment: 108 - Completed treatment: 88 - Withdrawals/losses to followup: 20 (14 due to AEs, 6 for unspecified reasons) Age: Mean (SD): NR Median: NR Range: NR **Sex (n [%]):** Female: 50% Male: 50% Race/ethnicity (n [%]): NR **Baseline blood pressure:** Seated trough office BP assessed using a standard mercury sphygmanometer; mean of 3 measurements taken after subject rested for 10 min Losartan / Enalapril SBP 155 ± 14 / 155 ± 15 DBP 100 ± 9 / 99 ± 9	**1) Blood pressure:** Mean trough seated BP on treatment (avg. 3.3 yr): Losartan / Enalapril SBP 140 ± 14 / 140 ± 18 DBP 90 ± 8 / 87 ± 7 All pre-/post- differences p < 0.01 Between-group p-values NR Also report 24-hr ABPM data **2) Rate of use of a single antihypertensive agent for BP control:** Number of patients (%) not taking adjunctive HCTZ: Losartan: 12 (55%) Enalapril: 32 (48%) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Withdrawals due to AEs: Losartan: 2 (headache, gastric distress) Enalapril: 12 (all cough) **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** Mean total cholesterol (mmol/L):	**General comments:** - Baseline characteristics of patients NR Quality assessment: Overall rating: Poor Comments: - No baseline characteristics reported - No detail about extent of followup (only give average of 3.3 yr) **Applicability:** - No baseline patient characteristics described or compared - Little detail about selection of case-controls, reasons for exclusion from eligible patients - Duration of therapy not defined at all

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results			Comments/ quality/applicability
		Concurrent medications (n [%]):	Baseline	Followupp-value		
	Duration of post-treatment followup: NA	NR	Losartan 5.09 ± 0.79	5.23 ± 0.86	NS	
			Enalapri 5.51 ± 0.93	5.92 ± 0.92	NS	
		Comorbidities (n [%]): NR				
			Mean HDL cholesterol (mmol/L):			
		Recruitment setting:	Baseline	Followup	p-value	
		- from PIUMA (Progetto Ipertensione Umbria Monitoaggio Ambulatoriale) study [ref 4, 14 in paper]	Losartan 1.26 ± 0.30	1.30 ± 0.21	NS	
			Enalapril 1.24 ± 0.28	1.28 ± 0.32	NS	
		Inclusion criteria:				
		- Office SBP ≥ 140 and/or DBP ≥ 90 on ≥ 3 visits	Mean LDL cholesterol (mmol/L):			
		- ≥1 valid BP measurement within 24h before enrollment	Baseline	Followup	p-value	
			Losartan 3.42 ± 0.79	3.32 ± 0.82	NS	
		Exclusion criteria:	Enalapril 3.59 ± 0.85	3.77 ± 0.86	NS	
		- Previous antihypertensive therapy or drugs withdrawn from ≥ 4 wk	Mean triglycerides (mmol/L):			
		- Evidence of CHF, CAD, significant valvular defects	Baseline	Followup	p-value	
		- Secondary causes of HTN	Losartan 1.23 ± 0.49	1.34 ± 0.56	NS	
		- "Other concomitant important disease"	Enalapril 1.47 ± 0.78	1.78 ± 0.86	NS	
			9) Progression to type 2 diabetes: NR			
			10) Markers of carbohydrate metabolism/diabetes control:			
			Mean glucose (mmol/L):			
			Baseline	Followup	p-value	
			Losartan 5.36 ± 0.65	5.31 ± 0.61	NS	
			Enalapril 5.56 ± 0.88	5.61 ± 0.90	NS	
			11) LV mass/function:			
			LV mass (g/BSA [m^2]):			

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Baseline / Followup / p-value Losartan 98 ± 18 / 87 ± 19 / <0.001 Enalapril 98 ± 20 / 89 ± 20 / <0.001 Similar results with LV mass in g/height Also report multiple other echo measurements including - IVS thickness, LV internal diam, PW thickness, endocardial shortening fraction, midwall shortening fraction, peak E/A ratio **12) Creatinine/GFR:** Mean creatinine (mmol/L): Baseline / Followup / p-value Losartan 85.7 ± 10.4 / 83.9 ± 12.9 / NS Enalapril 82.8 ± 14.7 / 93.2 ± 75.6 / NS Note - SD for enalapril on f/u must be a typo **13) Proteinuria:** NR	
Veronesi, Cicero, Prandin, et al., 2007 **#148**	Geographical location: Bologna, Italy Study dates: NR Funding source: NR Interventions: Randomized to: - ACEI (n = 61) - ARB (n = 53) - Calcium channel blocker (n = 63) - Diuretic (n = 63)	Number of patients: N = 347 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NR - Began treatment: NR - Completed treatment: 347 - Withdrawals/losses to followup: NR Age: Mean (SD): 59.4 ±6 **Sex (n [%]):** Female: 141 (40.6%)	**1) Blood pressure:** Change (by inference, time of second BP reading was at the 24 month followup) ACEI / ARB SBP: -10.5 / -11.2 DBP: -5.1 / -5.8 No statistically significant difference between classes of drugs. **2) Rate of use of a single antihypertensive agent for BP control:** 78.1% of entire sample (breakdown by drug	**General comments:** - No information reported on number of patients enrolled, number randomized, number of withdrawals, or reasons for loss to followup or exclusion after enrollment - No details on names and dosages of study medications, thereby making it impossible to interpret potential therapeutic dosages of study medications Quality assessment:

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Beta-blocker (n = 61) Sample sizes above are for patients who completed the study. Number of patients initially allocated to each drug class was NR. Name and dosage of medications NR Were additional anti-hypertension medications allowed: Yes; combination treatment was used in 15/347 patients (4%) If Yes to above, was this done: Per protocol (second medication [class NR] added if < 10% reduction of SBP by monotherapy after 6 months of treatment Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment adequate?: No Baseline/run-in period: None Duration of treatment: 24 months Duration of post-treatment	Male: 206 (59.4%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Resting and supine by mercury sphygmomanometer, mean of 3 readings 1 minute apart. ACEI ARB SBP: 152.5 ± 12 154.3 ± 13 DBP: 98.7 ± 8 99.1 ± 7 **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: - Uncomplicated mild to moderate HTN (SBP 140-159 mmHg and DBP 90-109 mmHg) - Age > 8 and ≤ 80 - No antihypertensive treatment during last 6 months - No history of major cardiovascular diseases (previous stroke, MI, heart failure, major arrhythmias) requiring complex pharmacological treatment - No history of intolerance or hypersensitivity for specific classes of antihypertensive drugs - Lack of compelling indications for a specific class of antihypertensive drugs according to ESH-ESC Guidelines (ESH-	class NR) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Persistence with antihypertensive treatment defined as the continued use of medications according to initial prescription over the period of followup. In patients in whom treatment was discontinued before the end of followup, persistence quantified as the time interval between randomization and treatment discontinuation. "Not persistent" patients included those who withdrew from treatment or those who were switched to a different class of drugs After 24 months: ACEI: 64.5% ARB: 68.5% No statistically significant difference between classes of antihypertensives Mean duration of persistence: ACEI: 18.7 ± 8 months ARB: 20.3 ± 9 months In logistic regression model of persistence on treatment using ARBs as referent, patients taking ACEIs were more likely to continue their initial antihypertensive therapy: OR 0.94; 95% CI 0.79 to 0.99	Overall rating: Poor Comments: - Inadequate reporting in many areas, including patient characteristics, patient flow (including screening, randomization, and withdrawal information) and name and dosages of study medications - Unblinded study **Applicability:** - Poor generalizability due to inadequate reporting of patient population, interventions, and results - Insufficient details about study medications, including name and dosage - Insufficient reporting about comorbidities and cointerventions

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	followup: None; last followup after 24 months of treatment	ESC 2003) - Capacity to comply with study protocol Exclusion criteria: - Secondary causes of HTN - Patients who needed a 3rd drug to control HTN were excluded from analysis after enrollment	**8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Williams, Gosse, Lowe, et al., 2006 **#296**	Geographical location: 75 centers Austria, France, Germany, Netherlands, South Africa, Spain , Switzerland, and United Kingdom Study dates: NR Funding source: NR Interventions: - Telmisartan 40 mg initial dose and forced titration to 80 mg after 2 wk (n = 397) - Ramipril 5 mg for 8 wk and then force titrated to ramipril 10 mg for the last 6 wk (n = 404) Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No - Assessors of outcomes: Yes	Number of patients: - Screened for inclusion: 1593 - Eligible for inclusion: 801 - Randomized: 801 - Began treatment: 801 - Completed treatment: 714 - Withdrawals/losses to followup: 57, 37 due to AEs, 10 due to lack of efficacy, 10 withdrew consent (note: reported numbers do not total correctly) Age: Mean (SD): 53.6 (10.6) ≥ 65: 131 (16%) **Sex (n [%]):** Female: 322 (41.2%) Male: 479 (59.8) Race/ethnicity (n [%]): White 621 (77.5%) Black 14 (1.7%) Mongoloid 7 (0.9%) Missing 159 (19.9%) **Baseline blood pressure:**	**1) Blood pressure:** Changes in trough seated BP from baseline to 14 wk: Reductions were greater with telmisartan 80 mg than with ramipril 10 mg by 4.6 mm Hg for SBP ($p < 0.0001$) and by 2.2 mm Hg for DBP ($p = 0.0002$). Pre-/post-treatment mean values NR. Seated DBP response (DBP < 90 mm Hg or reduction from baseline of ≥ 10 mm Hg): Telmisartan: 61.9% Ramipril: 54.8% ($p = 0.03$) Seated SBP response (SBP < 140 mm Hg or reduction from baseline of ≥ 10 mm Hg): Telmisartan: 76.2% Ramipril: 66.9% ($p = 0.004$) DBP response defined as DBP < 90 mm Hg or reduction from baseline $\geq$ 10 mm Hg; SBP response defined as SBP < 140 or reduction $\geq$ 10	**General comments:** - Titrations at different times so that telmisartan is titrated up and to higher relative dose than ramipril - No discussion outside of forced titration of BP checks during study and if any additional agents or if SBP very high what was done Quality assessment: Overall rating: Fair Comments: - No clear concealment of randomization - Not blinded - Titrated drugs at different times **Applicability:** Excludes so many patients that patients with heart disease or patients with many comorbidities would be excluded from the trial

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Was allocation concealment adequate?: NR Baseline/run-in period: 2- to 4-wk single-blind placebo run-in phase in which prior antihypertensives were discontinued Duration of treatment: 14 wk Duration of post-treatment followup: NR	Seated trough BP measured in triplicate using a manual sphygmomanometer according to ASH guidelines Telmisartan / Ramipril SPB 158.5 ± 11.9 / 158.3 ± 12.5 DBP 100.1 ± 4.9 / 100.1 ± 4.9 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** Clinic setting Inclusion criteria: - Age ≥ 18 - Mean seated DBP of 95-109 mm Hg measured using a manual sphygmomanometer (mean of 3 measurements taken 2 min apart) - 24-hr ABP of DBP ≥ 85 mm Hg after run-in period Exclusion criteria: - Known or suspected history of coronary disease, stroke, congestive heart failure, or recent acute cardiovascular event, secondary hypertension, poorly controlled insulin-dependant diabetes mellitus, or chronic kidney disease - Premenopausal women not	Also report BP in last 6 hours of 24 hours of ABPM at 14 weeks, as follows: Telmisartan / Ramipril SBP (SD) 128.7 (15.4) / 132.7 (14.8) SBP change (SD) -11.5 (11.7) / -8.2 (8.3) DBP (SD) 79.6 (9.3) / 81.7 (9.1) DBP change (SD) -8.2 (8.3) / -5.4 (7.7) Adj. SBP change* (SEM) -12.1 (.65) / -8.4 (.64) Adj. DBP change* (SEM) -8.5 (.44) / -5.8 (.43) * From model including main effects of treatment and 24 hr BP monitoring SBP difference (SEM) (telmisartan-ramipril): -3.7; SEM: 0.85; 95% CI: -5.4 to -2.0; P < 0.0001 DBP difference (SEM) (telmisartan-ramipril): -2.7; SEM: 0.57; 95% CI: -3.8 to -1.5; P < 0.0001 "Per-protocol analysis of the reduction from baseline in DBP confirmed that telmisartan 80 mg was superior to ramipril 5 mg (p < 0.0001) and 10 mg (p < 0.0001) in reducing the last 6-hour mean ambulatory DBP." **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** There were no deaths during the study.	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		using adequate contraception - Night shift workers	**4) Morbidity:** NR **5) Safety:** Any AE: Telmisartan: 153/397 (38.5%) Ramipril: 162/404 (40.1%) Severe AEs: Telmisartan: 13 (3.3%) Ramipril: 17 (4.2%) Drug-related AEs: Telmisartan: 6.5% Ramipril: 10.1% Drug-related serious AEs: 0 **6) Specific adverse events:** Drug-related AEs with incidence greater than 1% (fatigue, dizziness, HA, and cough) occurred in 14 (3.5%) telmisartan vs. 23 (5.7%) ramipril patients Cough: 2 (0.5%) telmisartan vs. 23 (5.7%) ramipril **7) Persistence/adherence:** Adherence monitored at each visit by counting the number of returned tablets. Noncompliant patients discontinued from rest of study but included in ITT analysis. Compliance with treatment was high (> 98.8%) in both groups – recognize this is in 714/801 patients that completed study 5 patients in each group withdrew because of lack of efficacy	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			21 in the telmisartan and 16 in the ramipril group withdraw because of AEs **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Wogen, Kreilick, Livornese, et al., 2003 **#1627**	Geographical location: U.S. ("geographically diverse" claims database) Study dates: Aug 1998 – Jul 2000 Funding source: Novartis Pharmaceuticals, Inc. Interventions: Lisinopril (n = 40,238) Valsartan (n = 29,669) Amlodipine (n = 73,148) Study design: Retrospective cohort study Blinding: - Patients: No - Providers: No - Assessors of outcomes: No Was allocation concealment	Number of patients: - Screened for inclusion: 14.6 million - Eligible for inclusion: 142,945 - Randomized: NA - Began treatment: 142,945 - Completed treatment: NA - Withdrawals/losses to followup: NA Age: Mean (SD): 63.1 (14.0) Median: NR Range: NR **Sex (n [%]):** Female: 53% Male: 47% Race/ethnicity (n [%]): NR; database stated to be "demographically diverse" **Baseline blood pressure:** NR	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Discontinuation was defined as a 60+ day period without a new prescription; persistence was defined as the absence of discontinuation. Discontinuation was examined directly and also in a Cox model that controlled for age, sex, chronic disease burden, and use of other antihypertensive agents. The results of this modeling were similar to the unadjusted results.	**General comments:** None Quality assessment: Overall rating: Fair Comments: - Non-random allocation to drugs - Differences noted in comorbidity between valsartan-treated patients and those on other antihypertensive drugs - Funded by pharmaceutical company **Applicability:** - Study period soon after introduction of ARBs; early use may not reflect current use patters

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	adequate?: NA Baseline/run-in period: NA Duration of treatment: NA Duration of post-treatment followup: 1 yr	**Concurrent medications (n [%]):** Concurrent cardiovascular meds: Diuretics: 35% Antihyperlipidemics: 32% Beta-blockers: 25.5% Antiplatelets: 14% Nitrates: 15% Digitalis: 9% Diuretic combination: 8% Valsartan patients significantly less likely to be prescribed these meds than patients in other two groups. **Comorbidities (n [%]):** Mean Chronic Disease Score (± SD) was 10.15 ± 6.00 for the entire cohort and was essentially comparable for all groups A significantly smaller proportion of valsartan patients was classified as having a "severe" chronic disease burden (35% vs. 31% for both lisinopril and amlodipine; p < 0.0001) **Recruitment setting:** Administrative pharmacy claims database from a large pharmacy benefits manager. Described as a "demographically and geographically diverse database that contains 3 years of longitudinal pharmacy claims data representing the payer mix in the U.S. health care market,	Compliance was not measured directly, but instead was estimated as the total days' supply of all prescriptions divided by the length of therapy. Predictors of non-compliance included older age, female sex, high chronic disease scores, use of lipid medications, use of beta-blockers, and use of nitrates. <u>1-yr persistence</u> <u>Compliance</u> Lisinopril 50% 86.3% Valsartan 63% 88.5% Amlodipine 53% 86.7% **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		including drug-insured lives from health care insurance carriers, managed care organizations, employers, and retirement and government plans." Inclusion criteria: - Continuously benefit-eligible for both mail-order and community pharmacy prescriptions between 1 Aug 1997 and 31 Jul 2000 - Initial prescription for one of 3 study drugs between 1 Aug 1998 and 31 Jul 1999 - New to therapy within the drug class (patients who received a prescription for a drug from the same class in the preceding 12 mo were excluded) Exclusion criteria: None specified		
Xu, Liu, Ji, et al., 2007 **#1288**	Geographical location: China Study dates: Jan-Dec 2006 Funding source: NR Interventions: Telmisartan 80 mg/day (n = 46) Enalapril 10 mg/day (n = 50) Were additional anti-hypertension medications allowed: NR Study design: RCT, parallel-group	Number of patients: N = 96 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 96 - Began treatment: 96 - Completed treatment:94 - Withdrawals/losses to followup: 2 in enalapril group for cough Age: Mean (SD): 51.2 ± 9.6 Range: 42 - 65 **Sex (n [%]):** Female: 34 (35.4%) Male: 62 (64.6%)	**1) Blood pressure:** <u>SBP (mmHg):</u> Telmisartan: Pre-therapy: 149.2 ± 5.02 3 months: 136.3 ± 4.7 6 months: 135.9 ± 3.9 Enalapril: Pre-therapy: 148.6 ± 4.4 3 months: 137.0 ± 5.1 6 months: 136.0 ± 7.0 <u>DBP (mmHg):</u> Telmisartan: Pre-therapy: 98.2 ± 7.2 3 months: 90.0 ± 2.8*	**General comments:** None Quality assessment: Overall rating: Poor Comments: No information about other medications, how randomization was done, or AEs that did not cause withdrawals **Applicability:** - No information about randomization process or blinding - No information about comorbidities or use of other medications

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Blinding: - Patients: NR - Providers: NR - Assessors of outcomes: NR Was allocation concealment adequate?: NR Baseline/run-in period: NR Duration of treatment: 6 months Duration of post-treatment followup: No followup after 6 months reported	Race/ethnicity (n [%]): NR **Baseline blood pressure:** Sitting blood pressure was measured in the right upper brachial artery for 3 times with an appropriate mercury sphygmomanometer, after at least 10 minutes of rest Telmisartan: SBP(mmHg) 149.24 ± 5.02 DSP (mmHg) 98.2 ± 7.20 Enalapril: SBP(mmHg) 148.6 ± 4.43 DSP (mmHg) 99.12 ± 2.97 **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR Inclusion criteria: Hypertensive outpatients with abnormal blood lipids according to WHO standard Exclusion criteria: - Secondary HTN - Renal insufficiency - DM - Acute coronary syndrome	6 months: 88.1 ± 3.0 Enalapril: Pre-therapy: 99.1 ± 3.0 3 months: 89.3 ± 3.0 6 months: 87.2 ± 4.1 **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** None **4) Morbidity:** NR **5) Safety:** Cough reported in 2 patients in enalapril group significant enough to cause withdrawal. No other adverse events reported. **6) Specific adverse events:** Cough reported in 2 patients in enalapril group significant enough to cause withdrawal. No other adverse events reported. **7) Persistence/adherence:** Except for 2 patients described above, all other patients completed 6 months of treatment **8) Lipid levels:** <u>Total cholesterol (TC; mmol/L):</u> Telmisartan: Pre-therapy: 6.1 ± 1.9 3 months: 6.0 ± 0.7 6 months: 5.8 ± 0.8	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Enalapril: Pre-therapy: 6.1 ± 1.0 3 months: 6.0 ± 1.1 6 months: 5.9 ± 1.1 <u>Triglycerides (TG; mmol/L):</u> Telmisartan: Pre-therapy: 2.8 ± 1.2 3 months: 2.4 ± 0.8 6 months: 2.0 ± 0.6 Enalapril: Pre-therapy: 2.8 ± 1.0 3 months: 2.7 ± 0.9 6 months: 2.6 ± 0.9 <u>LDL cholesterol (mmol/L):</u> Telmisartan: Pre-therapy: 3.1 ± 0.8 3 months: 2.7 ± 1.0 6 months: 2.3 ± 0.9 Enalapril: Pre-therapy: 3.1 ± 1.0 3 months: 2.7 ± 1.0 6 months: 2.3 ± 0.9 <u>HDL cholesterol (mmol/L):</u> Telmisartan: Pre-therapy: 1.4 ± 0.7 3 months: 1.5 ± 0.9 6 months: 1.65 ± 0.9 Enalapril: Pre-therapy: 1.4 ± 0.7 3 months: 1.4 ± 0.8 6 months: 1.4 ± 1.0 The level of TG in the telmisartan group decreased obviously after 3-month	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			treatment compared with that of pre-therapy and the enalapril group (P < 0.05), and the level of TG decreased more significantly after 6-month treatment (P < 0.01). The level of HDL cholesterol was significantly higher after 6-month treatment in the telmisartan group than pre-therapy and in the enalapril group (P < 0.05). **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** <u>Fasting blood glucose (mmol/L):</u> Telmisartan: Pre-therapy: 4.5 ± 0.5 3 months: 4.6 ± 0.5 6 months: 4.6 ± 0.6 Enalapril: Pre-therapy: 4.6 ± 0.5 3 months: 4.7 ± 0.5 6 months: 4.7 ± 0.5 <u>HOMA-IS (mU/L):</u> Telmisartan: Pre-therapy: 2.2 ± 0.4 3 months: 1.9 ± 0.3 6 months: 1.6 ± 0.3 Enalapril: Pre-therapy: 2.1 ± 0.3 3 months: 2.0 ± 0.3 6 months: 2.0 ± 0.3 HOMA-IS and HOMA-IR in the telmisartan group were significantly lower than pre-therapy and in the enalapril group after 3-month treatment (P < 0.05). HOMA-IS,	

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			HOMAIR, and P2HBG in the telmisartan group decreased significantly after 6-month treatment compared with pre-therapy and with the enalapril group (P < 0.01, P < 0.01, P < 0.05). HOMA-IS and HOMA-IR in the telmisartan group were lower after 6- month treatment than they were after 3-month treatment (P < 0.05). **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Yilmaz, Sonmez, Caglar, et al., 2007 **#212**	Geographical location: Etlik-Ankara, Turkey Study dates: 2004-2006 Funding source: NR Interventions: - Metoprolol 100 mg (n = 18) - Amlodipine 10 mg (n = 20) - Doxazosin 4 mg (n = 18) - Ramipril 5 (n = 20) - Valsartan 80 mg (n = 20) Were additional anti-hypertension medications allowed: No (not explicitly stated, but implied) Study design: RCT, parallel-group Blinding: - Patients: No - Providers: No	Number of patients: N = 96 - Screened for inclusion: 224 - Eligible for inclusion: NR - Randomized: 96 - Began treatment: 96 - Completed treatment: 96 - Withdrawals/losses to followup: 0 (but whether some patients discontinued treatment was NR) Ambiguous reporting of how many patients began and completed the run-in period Age: Mean (SD): 47.88 ± 5.29 **Sex (n [%]):** Female: 48 (50%) Male: 48 (50%) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Mean of 3 arm BP cuff readings	**1) Blood pressure:** <u>BP at 3 months:</u> Ramipril: SBP 136.10 (SD 5.09) DBP 87.65 (SD 3.80) Valsartan SBP 129.70 (SD 8.12) DBP 85.55 (SD 4.35) **2) Rate of use of a single antihypertensive agent for BP control:** NR (by inference, all patients were prescribed a single antihypertensive agent) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR	**General comments:** - Sample drawn from nephrology clinics that referred patients with metabolic syndrome who had not previously received treatment - Patients reportedly were unaware that they had HTN - Screening process and results not adequately reported - Final sample may not be representative of a larger clinical population Quality assessment: Overall rating: Poor Comments: - Unblinded - Randomization protocol poorly described - Small sample size - Poor reporting of outcomes by drug **Applicability:**

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Assessors of outcomes: NR Was allocation concealment adequate?: No. "…we stratified patients according to the above parameters [age, gender, BMI] in to similar groups and then assigned each group one of the study drugs" Baseline/run-in period: Up to 3 weeks of observation. Whether any patients became ineligible during the run-in period is NR. Duration of treatment: 3 months Duration of post-treatment followup: None (last followup at end of 3-month treatment)	in the morning in a resting condition. Ramipril: SBP 152.60 (SD 8.92) DBP 93.20 (SD 3.27) Valsartan SBP 157.55 (SD 7.08) DBP 94.60 (SD 3.40) **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** Referred by outpatient nephrology clinics Inclusion criteria: HTN (SBP ≥ 140 mmHg, DBP ≥ 90 mmHg) and at least 2 of the following: high triglycerides (> 150 mg/dL); low HDL (< 40 mg/dL for men and < 50 for women); high blood glucose > 100 mg/dL; high waist circumference (> 102 for men and > 88 for women) Exclusion criteria: - Currently taking any drugs including supplemental vitamin tablets and OTC drugs - Coronary artery disease (history of revascularization, ischemic ST segment alterations, or ECG criteria for left ventricular hypertrophy) - Diabetes mellitus	**8) Lipid levels:** <u>Baseline (mmol/L [SD]):</u> Ramipril: Triglycerides: 8.78 (1.86) Total cholesterol: 14.31 (2.16) LDL: 7.34 (1.45) HDL: 2.01 (0.30) Valsartan Triglycerides: 10.95 (3.19) Total cholesterol: 14.90 (2.29) LDL: 7.74 (2.02) HDL: 1.92 (0.25) <u>At 3-mo followup (mmol/L [SD])</u>: Ramipril: Triglycerides: 7.57 (1.95) Total cholesterol: 11.97 (1.83) LDL: 5.47 (1.06) HDL: 2.37 (0.32) Valsartan Triglycerides: 8.87 (2.39) Total cholesterol: 12.57 (2.50) LDL: 6.09 (1.85) HDL: 2.32 (0.29) P < 0.05 for all changes from baseline within groups, but comparison between groups was not reported **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** <u>Baseline:</u> Ramipril: Adiponectin (microgram/L [SD]): 9.38 (2.61) Insulin (mircoU/mL [SD]): 6.88 (1.08)	- Inadequate description of patient population - Inadequate reporting of patient flow and co-interventions

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Serum creatinine > 1.2 mg/dL	HOMA: 1.59 (0.71) Fasting glucose (mmol/L [SD]): 5.22 (0.46) Valsartan: Adiponectin (microgram/L [SD]): 8.50 (2.60) Insulin (mircoU/mL [SD]): 6.83 (1.26) HOMA: 1.60 (0.83) Fasting glucose (mmol/L [SD]): 5.38 (0.44) <u>At 3-month followup:</u> Ramipril: Adiponectin (microgram/L [SD]): 14.54 (3.82) Insulin (mircoU/mL [SD]): 5.80 (0.93) HOMA: 1.33 (0.54) Fasting glucose (mmol/L [SD]): 1.33 (0.54) Valsartan: Adiponectin (microgram/L [SD]): 14.40 (3.19) Insulin (mircoU/mL [SD]): 5.07 (1.42) HOMA: 1.15 (0.73) Fasting glucose (mmol/L [SD]): 5.11 (0.47) **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Yokoyama, Yang, Preblick, et al., 2007 **#210**	Geographical location: 4 commercial managed care health plans located in Northeast, Midwest, and Western US. Study dates: May 1, 2001, to Feb 28, 2003 Funding source: Novartis	Number of patients: STEP therapy cohort N = 6758 - Screened for inclusion: 1,000,000 - Eligible for inclusion: 6758 - Randomized: NA - Began treatment: 6758 - Completed treatment: NA - Withdrawals/losses to followup: NA	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** Rates of monotherapy reported, but comparison is between stepped care and comparison (not ACE vs. ARB) **3) Mortality:** NR	**General comments:** Cost data was also reported Quality assessment: Overall rating: Poor Comments: None **Applicability:** - Low-quality pharmacy claims

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Pharmaceuticals Corp. Interventions: Comparison of step-therapy program in 3 health plans in which a claim for an ARB triggered an electronic search of the patient's data for either an ACEI or an ARB in the preceding 3 months. The ARB claim was rejected if there was no prior use of ACEI/ARB in this timeframe and either pharmacist or patient had to contact prescriber to obtain an alternative to the ARB or a prior authorization (e.g., evidence that patient had attempted ACEI previously). The comparison group did not have a step-therapy program and used a tiered co-payment system Were additional anti-hypertension medications allowed: Yes If Yes to above, was this done: At discretion of clinician/investigator Study design: Other – retrospective cohort study Blinding: No Was allocation concealment adequate?: NA Baseline/run-in period: NA	Comparison cohort N = 33,709 - Screened for inclusion: 2,000,000 - Eligible for inclusion: 33,709 - Randomized: NA - Began treatment: 33,709 - Completed treatment: NA - Withdrawals/losses to followup: NA Age: Step therapy cohort: Mean (SD): 52.9 (11.2) **Comparison group:** Mean (SD): 57.6 (13.4) **Sex (n [%]):** **Step therapy cohort:** Male: 3652 (54.0) Female: 3106 (46.0) **Comparison group:** Female: 15355 (45.6) Male: 18354 (54.4) Race/ethnicity (n [%]): NR **Baseline blood pressure:** NR **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** Chronic disease score (SD): Step-therapy: 1598.3 (2089.83) Comparison: 1860.95 (2300.41) **Recruitment setting:** Pharmacy claims data from 4 health plans	**4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Among patients initiated on ACEI, proportion who switch to or added ARB within 12 months: Step care group: 333/5462 (6.1%) Comparison: 1811/25012 (7.2%) *Note, no information given on switch to other medication classes, so likely underestimates switch rate to other medicine* Of those whose ARB request was denied and who were instead given an ACEI, proportion switching to ARB within 12 months (combining ACE mono and combo therapy): 54/192 (28%) **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	data that does not capture current or prior adverse reactions, reasons for switching, or relevant comorbidities - Authors reported switch results as "switch to or added ARB" (emphasis ours) - Nearly ½ of denied ARB claims were overturned and patient received ARB. Some of these patients may have been ACEI-intolerant, but not captured in database records

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Duration of treatment: Minimum 12-month followup data Duration of post-treatment followup: NA	Inclusion criteria: **Step therapy cohort selection:** - Members from one of 3 participating health plans with step therapy - Age ≥ 18 years - Either started on an ACEI or were rejected for ARB during 6-month identification period - Continuously enrolled in the 3 months prior to and 12 months following the index date - No ACEI or ARB claims in the 3 months preceding new start **Comparison group selection:** - Members of the participating health plan - Age ≥ 18 years - Started on either an ACEI or an ARB during 6-month identification period - Continuously enrolled in the 3 months prior to and 12 months following the index date - No ACEI or ARB claims in the 3 months preceding new start		
Zhu, Liu, Wang, et al., 2008 **#1220**	Geographical location: Jinan, People's Republic of China Study dates: Recruited June to Dec 2006 Funding source: This work was supported by Jinan Science and Technology Research Foundation, Jinan, China	Number of patients: N = 90 - Screened for inclusion: 156 - Eligible for inclusion: 90 - Randomized: 90 - Began treatment: 90 - Completed treatment: 82 - Withdrawals/losses to followup: 8 lost to follow up Age: Mean (SD):	**1) Blood pressure:** 12 week findings SBP (mmHg): Benazepril 128 ± 8 Valsartan 130 ± 9 DBP (mmHg): Benazepril 82 ± 7 Valsartan 80 ± 8	**General comments:** Main purpose of study was to explore relationship between transforming growth factor and kidney damage Quality assessment: Overall rating: Fair Comments: - Incomplete followup

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Interventions: - Benazepril 10 mg once daily (n = 30) - Valsartan 80 mg once daily (n = 30) - Benazepril 10 mg + valsartan 80 mg once daily (n = 30) Doses of medications were doubled after 2 weeks if BP > 140/90 Were additional anti-hypertension medications allowed: Yes If Yes to above, was this done: Per protocol (HCTZ added if BP not at goal after dose escalation) Study design: RCT, parallel-group, double-blind Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes Was allocation concealment adequate?: NR Baseline/run-in period: 1 week Duration of treatment: 12 weeks Duration of post-treatment followup: NA	Benazepril: 55 ± 11 Valsartan: 57 ± 10 **Sex (n [%]):** Female: 12/28 (benazepril), 11/27 (valsartan) Male: 16/28 (benazepril), 16/27 (valsartan) Race/ethnicity (n [%]): NR **Baseline blood pressure:** Blood pressure was taken as the mean of two to three independent measurements with at least 2-min separation obtained with a standard sphygmomanometer after 5 min of rest at clinic. A 24-h ambulatory blood pressure monitoring was also applied to record SBP and DBP for those who were admitted to the antihypertensive drug trial at baseline and 12 weeks. Benazepril: SBP (mmHg) 153 ± 11 DBP (mmHg) 95 ± 12 Valsartan: SBP (mmHg) 151 ± 10 DBP (mmHg) 93 ± 10 **Concurrent non-hypertension medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** All	Blood pressure (SBP and DBP) was significantly reduced after 12-week antihypertensive therapy in all the three groups compared to their baseline blood pressure values (P < 0.05). There were no significant differences in the reduction of blood pressure between the groups. **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** 2 benazepril patients withdrew because of cough **6) Specific adverse events:** See immediately above **7) Persistence/adherence:** 8 patients withdrew, 2 in the benazepril arm because of cough, 1 patient from the valsartan group because of failure of normalization of blood pressure, 4 patients due to failure to followup **8) Lipid levels:** There were no significant changes in lipids compared to the baseline values (data not shown) **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** There were no significant changes in	- Completers analysis **Applicability:** - Unclear how patients were chosen from original 156 patients in parent study

Evidence Table E1. Direct comparator studies of ACEIs, ARBs, and direct renin inhibitors (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		participants were recruited at Jinan Central Hospital Clinic Inclusion criteria: Stages 1 (SBP 140–159 mmHg and DBP 90–99 mmHg) and 2 (SBP 160–179 mmHg and DBP 100–109 mmHg) essential hypertension Exclusion criteria: - Infectious and inflammatory diseases - Presence of any form of secondary HTN - Heart failure with LVH - Diabetes mellitus - Metabolic disease - Hepatic disease - Renal disease - Malignancy	glucose compared to the baseline values (data not shown) **11) LV mass/function:** NR **12) Creatinine/GFR:** There were no significant changes in serum BUN and creatinine concentrations at the end of antihypertensive therapy (P > 0.05). BUN (mg/dL): Benazepril (baseline/12 week) 16.0 ± 5.1/15.7 ± 5.3 Valsartan (baseline/12 week) 15.7 ± 4.8/16.0 ± 5.0 Creatinine (mg/dL): Benazepril (baseline/12 week) 1.04 ± 0.12/1.06 ± 0.15 Valsartan (baseline/12 week) 1.05 ± 0.11/1.04 ± 0.14 **13) Proteinuria:** ACR (mg/g): Benazepril (baseline/12 week) 332 ± 66/215 ± 54 Valsartan (baseline/12 week) 324 ± 57/211 ± 52	

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Spoelstra-de Man AM, van Ittersum FJ, Schram MT, et al. Aggressive antihypertensive strategies based on hydrochlorothiazide, candesartan or lisinopril decrease left ventricular mass and improve arterial compliance in patients with type II diabetes mellitus and hypertension. J Hum Hypertens 2006;20(8):599-611.

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Tikkanen I, Omvik P, Jensen HA. Comparison of the angiotensin II antagonist losartan with the angiotensin converting enzyme inhibitor enalapril in patients with essential hypertension. J Hypertens 1995;13(11):1343-51.

Townsend R, Haggert B, Liss C, et al. Efficacy and tolerability of losartan versus enalapril alone or in combination with hydrochlorothiazide in patients with essential hypertension. Clin Ther 1995;17(5):911-23.

Uchiyama-Tanaka Y, Mori Y, Kishimoto N, et al. Comparison of the effects of quinapril and losartan on carotid artery intima-media thickness in patients with mild-to-moderate arterial hypertension. Kidney & Blood Pressure Research 2005;28(2):111-6.

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Veronesi M, Cicero AF, Prandin MG, et al. A prospective evaluation of persistence on antihypertensive treatment with different antihypertensive drugs in clinical practice. Vascular Health & Risk Management 2007;3(6):999-1005.

Williams B, Gosse P, Lowe L, et al. The prospective, randomized investigation of the safety and efficacy of telmisartan versus ramipril using ambulatory blood pressure monitoring (PRISMA I). J Hypertens 2006;24(1):193-200.

Wogen J, Kreilick CA, Livornese RC, et al. Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. Journal of Managed Care Pharmacy 2003;9(5):424-9.

Xu D, Liu J, Ji C, et al. Effects of telmisartan on hypertensive patients with dyslipidemia and insulin resistance. Journal of Geriatric Cardiology 2007;4(3):149-52.

Yilmaz MI, Sonmez A, Caglar K, et al. Effect of antihypertensive agents on plasma adiponectin levels in hypertensive patients with metabolic syndrome. Nephrology 2007;12(2):147-53.

Yokoyama K, Yang W, Preblick R, et al. Effects of a step-therapy program for angiotensin receptor blockers on antihypertensive medication utilization patterns and cost of drug therapy.[see comment]. Journal of Managed Care Pharmacy 2007;13(3):235-44.

Zhu S, Liu Y, Wang L, et al. Transforming growth factor-(beta)(1) is associated with kidney damage in patients with essential hypertension: Renoprotective effect of ACE inhibitor and/or angiotensin II receptor blocker. Nephrology Dialysis Transplantation 2008;23(9):2841-6.

Appendix F. Applicability Criteria

Instructions to abstractors/assessors: Do not assign an overall applicability score. Instead, list the most important (up to 3) limitations affecting applicability, if any, based on the following list.

Setting of the study

(1) In which country (or countries) was the study conducted?

(2) In what health care system (or systems) was the study conducted?

(3) Were patients recruited from the primary, secondary, or tertiary care settings?

(4) How were study centers selected for participation?

(5) How were study clinicians selected for participation?

Selection of participants

(6) How were participants diagnosed and identified for eligibility screening before random allocation?

(7) What were the study eligibility criteria?

(8) What were the study exclusion criteria?

(9) Did the study require a run-in period with the control or placebo intervention?

(10) Did the study require a run-in period with the active intervention?

(11) Did the study selectively recruit participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition?

(12) Did the study report the ratio of randomly allocated participants to nonallocated participants (who were eligible)?

(13) Did the study report the proportion of eligible participants who declined random allocation?

Characteristics of study participants

(14) Did the study report participants' baseline characteristics?

(15) Did the study report participants' race?

(16) Did the study report participants' underlying pathology?

(17) Did the study report participants' stage in the natural history of the disease?

(18) Did the study report participants' severity of disease?

(19) Did the study report participants' comorbid conditions?

(20) Did the study report participants' absolute risk of a poor outcome in the control arm?

Differences between the study protocol and routine clinical practice

(21) Were the study interventions (active arm) similar to interventions used in routine clinical practice?

(22) Was the timing of the intervention similar to the timing in routine clinical practice?

(23) Was the study's control arm appropriate and relevant in relation to routine clinical practice?

(24) Were the study's cointerventions—which were not randomly allocated—adequate to reflect routine clinical practice?

(25) Were any interventions prohibited by the study that are routinely used in clinical practice?

(26) Have there been diagnostic or therapeutic advances used in routine practice since the study was conducted?

Outcome measures and followup

(27) If applicable, did the study use a clinically relevant surrogate outcome?

(28) If applicable, did the study use a scale that is clinically relevant, valid, and reproducible?

(29) If applicable, was the intervention beneficial on the most relevant components of the composite outcome?

(30) Which clinician measured the outcome (e.g., treating physician or surgeon)?

(31) Did the study use patient-centered outcomes?

(32) How frequently were participants followed in the study?

(33) Was the duration of participant followup adequate?

Adverse effects of treatment

(34) How completely did the study report the occurrence of relevant adverse effects?

(35) Did the study report the rates of treatment discontinuations?

(36) Were the study centers and/or clinicians selected on the basis of their skill or experience?

(37) Did the study exclude participants at elevated risk of intervention complications?

(38) Did the study exclude participants who suffered adverse effects during the run-in period?

(39) Did the study monitor participants intensively for early signs of adverse effects?

Appendix G. List of Excluded Direct Comparator Studies

All studies listed below were either identified at the abstract screening stage as having treatment duration/length of followup less than 12 weeks or were reviewed in their full-text version and excluded. Following each reference is the reason for exclusion. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Akinboboye OO, Chou RL, Bergmann SR. Augmentation of myocardial blood flow in hypertensive heart disease by angiotensin antagonists: a comparison of lisinopril and losartan. J Am Coll Cardiol 2002;40(4):703-9. Exclude: N < 20.

Ali K, Rajkumar C, Fantin F, et al. Irbesartan improves arterial compliance more than lisinopril. Vascular Health & Risk Management 2009;5(4):587-92. Exclude: N < 20.

Alcocer L, Fernandez-Bonetti P, Campos E, et al. Clinical efficacy and safety of telmisartan 80 mg once daily compared with enalapril 20 mg once daily in patients with mild-to-moderate hypertension: results of a multicentre study. Int J Clin Pract Suppl 2004;(145):23-8. Exclude: Followup < 12 wk.

Almazov VA, Shlyakhto EV, Konrady AO, et al. Correction of hypertensive cardiac remodelling: comparison of different antihypertensive therapies. Med Sci Monit 2000;6(2):309-13. Exclude: N < 20.

Altiparmak MR, Trablus S, Apaydin S, et al. Is losartan as effective as enalapril on posttransplant persistent proteinuria? Transplant Proc 2001;33(7-8):3368-9. Exclude: Not essential hypertension.

Andersen S, Tarnow L, Rossing P, et al. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. Kidney Int 2000;57(2):601-6. Exclude: Followup < 12 wk.

Anderson RE, Pfeffer MA, Thune JJ, et al. High-risk myocardial infarction in the young: The VALsartan In Acute myocardial iNfarcTion (VALIANT) trial. American Heart Journal 2008;155(4):706-711. Full Text: Exclude - HTN outcomes not reported separately

Azizi M, Linhart A, Alexander J, et al. Pilot study of combined blockade of the renin-angiotensin system in essential hypertensive patients. J Hypertens 2000;18(8):1139-47. Exclude: Followup < 12 wk.

Aznaouridis KA, Stamatelopoulos KS, Karatzis EN, et al. Acute effects of renin-angiotensin system blockade on arterial function in hypertensive patients. Journal of Human Hypertension 2007;21(8):654-63. Full Text: Exclude - duration < 12 wks

Bakris G, Sica D, Ram V, et al. A comparative trial of controlled-onset, extended-release verapamil, enalapril, and losartan on blood pressure and heart rate changes. Am J Hypertens 2002;15(1 Pt 1):53-7. Exclude: Followup < 12 wk.

Bakris GL. ACE inhibitors and ARBs: are they better than other agents to slow nephropathy progression? Journal of Clinical Hypertension 2007;9(6):413-5. Full Text: Exclude - not a clinical trial

Barnett A. Preventing renal complications in type 2 diabetes: Results of the diabetics exposed to telmisartan and enalapril trial. Journal of the American Society of Nephrology 2006;17(SUPPL. 2):S132-S135. Full Text: Exclude - not a clinical trial

Bavanandan S, Morad Z, Ismail O, et al. A comparison of valsartan and perindopril in the treatment of essential hypertension in the Malaysian population. Med J Malaysia 2005;60(2):158-62. Exclude: Followup < 12 wk.

Benz J, Oshrain C, Henry D, et al. Valsartan, a new angiotensin II receptor antagonist: a double-blind study comparing the incidence of cough with lisinopril and hydrochlorothiazide. J Clin Pharmacol 1997;37(2):101-7. Exclude: Followup < 12 wk.

Bohm M, Baumhakel M, Probstfield JL, et al. Sexual function, satisfaction, and association of erectile dysfunction with cardiovascular disease and risk factors in cardiovascular high-risk patients: Substudy of the ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNT Study in ACE-INtolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND). American Heart Journal 2007;154(1):94-101. Full Text: Exclude - HTN outcomes not reported separately

Botero R, Matiz H, Maria E, et al. Efficacy and safety of valsartan compared with enalapril at different altitudes. Int J Cardiol 2000;72(3):247-54. Exclude: Followup < 12 wk.

Brown NJ, Kumar S, Painter CA, et al. ACE inhibition versus angiotensin type 1 receptor antagonism: differential effects on PAI-1 over time. Hypertension 2002;40(6):859-65. Exclude: Followup < 12 wk.

Byyny RL, Merrill DD, Bradstreet TE, et al. An inpatient trial of the safety and efficacy of losartan compared with placebo and enalapril in patients with essential hypertension. Cardiovasc Drugs Ther 1996;10(3):313-9. Exclude: Followup < 12 wk.

Cha YJ, Pearson VE. Angioedema due to losartan. Ann Pharmacother 1999;33(9):936-8. Exclude: Followup < 12 wk.

Chan P, Tomlinson B, Huang TY, et al. Double-blind comparison of losartan, lisinopril, and metolazone in elderly hypertensive patients with previous angiotensin-converting enzyme inhibitor-induced cough. J Clin Pharmacol 1997;37(3):253-7. Exclude: Followup < 12 wk.

Chanudet X, De Champvallins M. Antihypertensive efficacy and tolerability of low-dose perindopril/indapamide combination compared with losartan in the treatment of essential hypertension. Int J Clin Pract 2001;55(4):233-9. Exclude: Not ACEI vs. ARB.

Chapman AB, Torres VE, Perrone RD, et al. The HALT polycystic kidney disease trials: design and implementation. Clinical Journal of The American Society of Nephrology: CJASN 2010;5(1):102-9. Exclude - ACE + drug X versus ARB + drug Y

Chen JH, Cheng JJ, Chen CY, et al. Comparison of the efficacy and tolerability of telmisartan 40 mg vs. enalapril 10 mg in the treatment of mild-to-moderate hypertension: a multicentre, double-blind study in Taiwanese patients. Int J Clin Pract Suppl 2004;(145):29-34. Exclude: Followup < 12 wk.

Chen K, Chiou CF, Plauschinat CA, et al. Patient satisfaction with antihypertensive therapy. J Hum Hypertens 2005;19(10):793-9. Exclude: Followup < 12 wk.

Cheung R, Lewanczuk RZ, Rodger NW, et al. The effect of valsartan and captopril on lipid parameters in patients with type II diabetes mellitus and nephropathy. Int J Clin Pract 1999;53(8):584-92. Exclude: No separate results for subgroup with hypertension.

Chiou KR, Chen CH, Ding PY, et al. Randomized, double-blind comparison of irbesartan and enalapril for treatment of mild to moderate hypertension. Chung Hua I Hsueh Tsa Chih 2000;63(5):368-76. Exclude: Followup < 12 wk.

Chowta KN, Chowta MN, Bhat P, et al. An open comparative clinical trial to assess the efficacy and safety of losartan versus enalapril in mild to moderate hypertension. J Assoc Physicians India 2002;50:1236-9. Exclude: Followup < 12 wk.

Ciulla MM, Paliotti R, Esposito A, et al. Effects of antihypertensive treatment on ultrasound measures of myocardial fibrosis in hypertensive patients with left ventricular hypertrophy: results of a randomized trial comparing the angiotensin receptor antagonist, candesartan and the angiotensin-converting enzyme inhibitor, enalapril. Journal of Hypertension 2009;27(3):626-32. Full Text: Exclude - no outcomes of interest

Cowan BR, Young AA, Anderson C, et al. Left Ventricular Mass and Volume With Telmisartan, Ramipril, or Combination in Patients With Previous Atherosclerotic Events or With Diabetes Mellitus (from the ONgoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [ONTARGET]). American Journal of Cardiology 2009;104(11):1484-1489. Full Text: Exclude - HTN outcomes not reported separately

Critchley JA, Gilchrist N, Ikeda L, et al. A randomized, double-masked comparison of the antihypertensive efficacy and safety of combination therapy with losartan and hydrochlorothiazide versus captopril and hydrochlorothiazide in elderly and younger patients. Curr Ther Res Clin Exp 1996;57(5):392-407. Exclude: Could not obtain copy.

Cuocolo A, Storto G, Izzo R, et al. Effects of valsartan on left ventricular diastolic function in patients with mild or moderate essential hypertension: comparison with enalapril. J Hypertens 1999;17(12 Pt 1):1759-66. Exclude: Followup < 12 wk.

de la Sierra A, Gil-Extremera B, Calvo C, et al. Comparison of the antihypertensive effects of the fixed dose combination enalapril 10 mg/nitrendipine 20 mg vs losartan 50 mg/hydrochlorothiazide 12.5 mg, assessed by 24-h ambulatory blood pressure monitoring, in essential hypertensive patients. J Hum Hypertens 2004;18(3):215-22. Exclude: Followup < 12 wk.

Delles C, Jacobi J, John S, et al. Effects of enalapril and eprosartan on the renal vascular nitric oxide system in human essential hypertension. Kidney Int 2002;61(4):1462-8. Exclude: Followup < 12 wk.

Delles C, Schneider MP, John S, et al. Angiotensin converting enzyme inhibition and angiotensin II AT1-receptor blockade reduce the levels of asymmetrical N(G), N(G)-dimethylarginine in human essential hypertension. Am J Hypertens 2002;15(7 Pt 1):590-3. Exclude: Followup < 12 wk.

Derosa G, Ferrari I, Cicero AF. Irbesartan and hydrochlorothiazide association in the treatment of hypertension. Current Vascular Pharmacology 2009;7(2):120-36. Full Text: Exclude - not a clinical trial

Diamond JA, Gharavi A, Roychoudhury D, et al. Effect of long-term eprosartan versus enalapril antihypertensive therapy on left ventricular mass and coronary flow reserve in stage I-II hypertension. Eprosartan Study Group. Curr Med Res Opin 1999;15(1):1-8. Exclude: Could not obtain copy.

Donmez G, Derici U, Erbas D, et al. The effects of losartan and enalapril therapies on the levels of nitric oxide, malondialdehyde, and glutathione in patients with essential hypertension. Jpn J Physiol 2002;52(5):435-40. Exclude: Followup < 12 wk.

Donner KM, Hiltunen TP, Suonsyrja T, et al. CYP2C9 genotype modifies activity of the renin-angiotensin-aldosterone system in hypertensive men. Journal of Hypertension 2009;27(10):2001-9. Exclude - reported drug not on our list

Dowlatshahi D, Hill MD. Angiotensin receptor blockers and secondary stroke prevention: the MOSES study. Expert Review of Cardiovascular Therapy 2009;7(5):459-64. Full Text: Exclude - not a clinical trial

el-Agroudy AE, Hassan NA, Foda MA, et al. Effect of angiotensin II receptor blocker on plasma levels of TGF-beta 1 and interstitial fibrosis in hypertensive kidney transplant patients. Am J Nephrol 2003;23(5):300-6. Exclude: Not essential hypertension.

Erdem Y, Usalan C, Haznedaroglu IC, et al. Effects of angiotensin converting enzyme and angiotensin II receptor inhibition on impaired fibrinolysis in systemic hypertension. Am J Hypertens 1999;12(11 Pt 1):1071-6. Exclude: No outcomes of interest.

Erley CM, Bader B, Scheu M, et al. Renal hemodynamics in essential hypertensives treated with losartan. Clin Nephrol 1995;43 Suppl 1:S8-11. Exclude: Followup < 12 wk.

Fagard R, Lijnen P, Pardaens K, et al. A randomised, placebo-controlled, double-blind, crossover study of losartan and enalapril in patients with essential hypertension. J Hum Hypertens 2001;15(3):161-7. Exclude: Followup < 12 wk.

Falaschetti E, Chaudhury M, Mindell J, et al. Continued improvement in hypertension management in England: results from the Health Survey for England 2006.[see comment]. Hypertension 2009;53(3):480-6. Full Text: Exclude - no outcomes of interest/no direct comparison

Feldman RD, Zou GY, Vandervoort MK, et al. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial.[see comment]. Hypertension 2009;53(4):646-53. Full Text: Exclude - no direct comparison

Fogari R, Zoppi A, Carretta R, et al. Effect of indomethacin on the antihypertensive efficacy of valsartan and lisinopril: a multicentre study. J Hypertens 2002;20(5):1007-14. Exclude: Followup < 12 wk.

Fogari R, Zoppi A, Corradi L, et al. Comparative effects of lisinopril and losartan on insulin sensitivity in the treatment of non diabetic hypertensive patients. Br J Clin Pharmacol 1998;46(5):467-71. Exclude: Followup < 12 wk.

Fogari R, Zoppi A, Lazzari P, et al. ACE inhibition but not angiotensin II antagonism reduces plasma fibrinogen and insulin resistance in overweight hypertensive patients. J Cardiovasc Pharmacol 1998;32(4):616-20. Exclude: Followup < 12 wk.

Fox JC, Leight K, Sutradhar SC, et al. The JNC 7 approach compared to conventional treatment in diabetic patients with hypertension: a double-blind trial of initial monotherapy vs. combination therapy. J Clin Hypertens (Greenwich) 2004;6(8):437-42; quiz 443-4. Exclude: Followup < 12 wk.

Franchi F, Lazzeri C, Foschi M, et al. Cardiac autonomic tone during trandolapril-irbesartan low-dose combined therapy in hypertension: a pilot project. J Hum Hypertens 2002;16(8):597-604. Exclude: Followup < 12 wk.

Gainer JV, Morrow JD, Loveland A, et al. Effect of bradykinin-receptor blockade on the response to angiotensin-converting-enzyme inhibitor in normotensive and hypertensive subjects. N Engl J Med 1998;339(18):1285-92. Exclude: Followup < 12 wk.

Gansevoort RT, de Zeeuw D, de Jong PE. Is the antiproteinuric effect of ACE inhibition mediated by interference in the renin-angiotensin system? Kidney Int 1994;45(3):861-7. Exclude: Followup < 12 wk.

Geiger H, Barranco E, Gorostidi M, et al. Combination therapy with various combinations of aliskiren, valsartan, and hydrochlorothiazide in hypertensive patients not adequately responsive to hydrochlorothiazide alone. Journal of Clinical Hypertension 2009;11(6):324-32. Full Text: Exclude - Duration < 12 wks

Gleason PP. Assessing step-therapy programs:a step in the right direction.[see comment][comment]. Journal of Managed Care Pharmacy 2007;13(3):273-5. Full Text: Exclude - not a clinical trial

Goldberg MR, Bradstreet TE, McWilliams EJ, et al. Biochemical effects of losartan, a nonpeptide angiotensin II receptor antagonist, on the renin-angiotensin-aldosterone system in hypertensive patients. Hypertension 1995;25(1):37-46. Exclude: Followup < 12 wk.

Gosse P, Neutel JM, Schumacher H, et al. The effect of telmisartan and ramipril on early morning blood pressure surge: a pooled analysis of two randomized clinical trials. Blood Pressure Monitoring 2007;12(3):141-7. Full Text: Exclude - duplicate publication

Gradman AH, Arcuri KE, Goldberg AI, et al. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. Hypertension 1995;25(6):1345-50. Exclude: Followup < 12 wk.

Gradman AH, Schmieder RE, Lins RL, et al. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. Circulation 2005;111(8):1012-8. Full Text: Exclude - not a clinical trial

Grandi AM, Solbiati F, Laurita E, et al. Effects of dual blockade of Renin-Angiotensin system on concentric left ventricular hypertrophy in essential hypertension: a randomized, controlled pilot study. American Journal of Hypertension 2008;21(2):231-7. Full Text: Exclude - compares ACEIs/drugX vs ARBs/drugY

Guasti L, Petrozzino MR, Mainardi LT, et al. Autonomic function and baroreflex sensitivity during angiotensin-converting enzyme inhibition or angiotensin II AT-1 receptor blockade in essential hypertensive patients. Acta Cardiol 2001;56(5):289-95. Exclude: Followup < 12 wk.

Guasti L, Zanotta D, Diolisi A, et al. Changes in pain perception during treatment with angiotensin converting enzyme-inhibitors and angiotensin II type 1 receptor blockade. J Hypertens 2002;20(3):485-91. Exclude: Followup < 12 wk.

Han SW, Won YW, Yi JH, et al. No impact of hyperkalaemia with renin-angiotensin system blockades in maintenance haemodialysis patients. Nephrology Dialysis Transplantation 2007;22(4):1150-1155. Full Text: Exclude - duration < 12 weeks

Hannedouche T, Chanard J, Baumelou B, et al. Evaluation of the safety and efficacy of telmisartan and enalapril, with the potential addition of frusemide, in moderate-renal failure patients with mild-to-moderate hypertension. J Renin Angiotensin Aldosterone Syst 2001;2(4):246-54. Exclude: Followup < 12 wk.

Hartog JWL, Van De Wal RM, Schalkwijk CG, et al. Advanced glycation end-products, anti-hypertensive treatment and diastolic function in patients with hypertension and diastolic dysfunction. European Journal of Heart Failure 2010;12(4):397-403. Exclude - ACEI + drug X vs ARB + drug Y

Hasler C, Nussberger J, Maillard M, et al. Sustained 24-hour blockade of the renin-angiotensin system: a high dose of a long-acting blocker is as effective as a lower dose combined with an angiotensin-converting enzyme inhibitor. Clin Pharmacol Ther 2005;78(5):501-7. Exclude: Followup < 12 wk.

Haymore BR, Yoon J, Mikita CP, et al. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. Annals of Allergy, Asthma, & Immunology 2008;101(5):495-9. Exclude - meta-analysis for background

Heckbert SR, Wiggins KL, Glazer NL, et al. Antihypertensive treatment with ACE inhibitors or beta-blockers and risk of incident atrial fibrillation in a general hypertensive population. American Journal of Hypertension 2009;22(5):538-44. Full Text: Exclude - no direct comparison

Hedner T, Oparil S, Rasmussen K, et al. A comparison of the angiotensin II antagonists valsartan and losartan in the treatment of essential hypertension. Am J Hypertens 1999;12(4 Pt 1):414-7. Exclude: Followup < 12 wk.

Heran BS, Wong MMY, Heran IK, et al. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. Cochrane Database of Systematic Reviews 2009;4. Exclude - systematic review for background

Hillebrand U, Suwelack BM, Loley K, et al. Blood pressure, antihypertensive treatment, and graft survival in kidney transplant patients. Transplant International 2009;22(11):1073-80. Exclude - no outcomes of interest

Himmelmann A, Keinanen-Kiukaanniemi S, Wester A, et al. The effect duration of candesartan cilexetil once daily, in comparison with enalapril once daily, in patients with mild to moderate hypertension. Blood Press 2001;10(1):43-51. Exclude: Followup < 12 wk.

Hirschl MM, Bur A, Woisetschlaeger C, et al. Effects of candesartan and lisinopril on the fibrinolytic system in hypertensive patients. Journal of Clinical Hypertension 2007;9(6):430-5. Full Text: Exclude - duration < 12 wks

Holwerda NJ, Fogari R, Angeli P, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. J Hypertens 1996;14(9):1147-51. Exclude: Followup < 12 wk.

Hong L, Maoyin C, Ping C, et al. Comparison of losartan and benazepril for the treatment of mild and moderate essential hypertension. Acta Academiae Medicinae Hubei 2000;21(3):211-3. Exclude: Followup < 12 wk.

Hou FF, Xie D, Zhang X, et al. Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency.[see comment]. Journal of the American Society of Nephrology 2007;18(6):1889-98. Full Text: Exclude - results inadequately reported

Igarashi M, Hirata A, Kadomoto Y, et al. Dual blockade of angiotensin II with enalapril and losartan reduces proteinuria in hypertensive patients with type 2 diabetes. Endocrine Journal 2006;53(4):493-501. Full Text: Exclude - no direct comparison

Iimura O, Shimamoto K, Matsuda K, et al. Effects of angiotensin receptor antagonist and angiotensin converting enzyme inhibitor on insulin sensitivity in fructose-fed hypertensive rats and essential hypertensives. Am J Hypertens 1995;8(4 Pt 1):353-7. Exclude: Followup < 12 wk.

Ito A, Egashira K, Narishige T, et al. Renin-angiotensin system is involved in the mechanism of increased serum asymmetric dimethylarginine in essential hypertension. Jpn Circ J 2001;65(9):775-8. Exclude: Followup < 12 wk.

Jilma B, Li-Saw-Hee FL, Wagner OF, et al. Effects of enalapril and losartan on circulating adhesion molecules and monocyte chemotactic protein-1. Clin Sci (Colch) 2002;103(2):131-6. Exclude: Followup < 12 wk.

Jordan J, Engeli S, Boye SW, et al. Direct Renin inhibition with aliskiren in obese patients with arterial hypertension. Hypertension 2007;49(5):1047-55. Full Text: Exclude - duration < 12 weeks

Joshi SR, Yeolekar ME, Tripathi KK, et al. Evaluation of efficacy and tolerability of Losartan and Ramipril combination in the management of hypertensive patients with associated diabetes mellitus in India (LORD Trial). J Assoc Physicians India 2004;52:189-95. Exclude: Not ACEI vs. ARB.

Kaplan NM. Recent clinical trials: the good, the bad, and the misleading.[see comment]. Hypertension 2008;52(4):608-9. Full Text: Exclude - not a clinical trial

Kaplan NM. TROPHY: a trial that may change clinical practice. Current Hypertension Reports 2006;8(5):359-60. Full Text: Exclude - not a clinical trial

Karas M, Lacourciere Y, LeBlanc AR, et al. Effect of the renin-angiotensin system or calcium channel blockade on the circadian variation of heart rate variability, blood pressure and circulating catecholamines in hypertensive patients. J Hypertens 2005;23(6):1251-60. Exclude: Followup < 12 wk.

Karotsis AK, Symeonidis A, Mastorantonakis SE, et al. Additional antihypertensive effect of drugs in hypertensive subjects uncontrolled on diltiazem monotherapy: a randomized controlled trial using office and home blood pressure monitoring. Clinical & Experimental Hypertension (New York) 2006;28(7):655-62. Full Text: Exclude - Duration < 12 wks

Kashiwagi A. Reduction of microalbuminuria in patients with type 2 diabetes. The Shiga Microalbuminuria Reduction Trial (SMART). Diabetes Care 2007;30(6):1581-1583. Full Text: Exclude - study drug not on our list

Kim W, Lee S, Kang SK, et al. Effects of angiotensin converting enzyme inhibitor and angiotensin II receptor antagonist therapy in hypertensive renal transplant recipients. Transplant Proc 2002;34(8):3223-4. Exclude: Followup < 12 wk.

Kiski D, Stepper W, Brand E, et al. Impact of renin-angiotensin-aldosterone blockade by angiotensin-converting enzyme inhibitors or AT-1 blockers on frequency of contrast medium-induced nephropathy: a post-hoc analysis from the Dialysis-versus-Diuresis (DVD) trial. Nephrology Dialysis Transplantation 2010;25(3):759-64. Exclude - results don't report HTN separately

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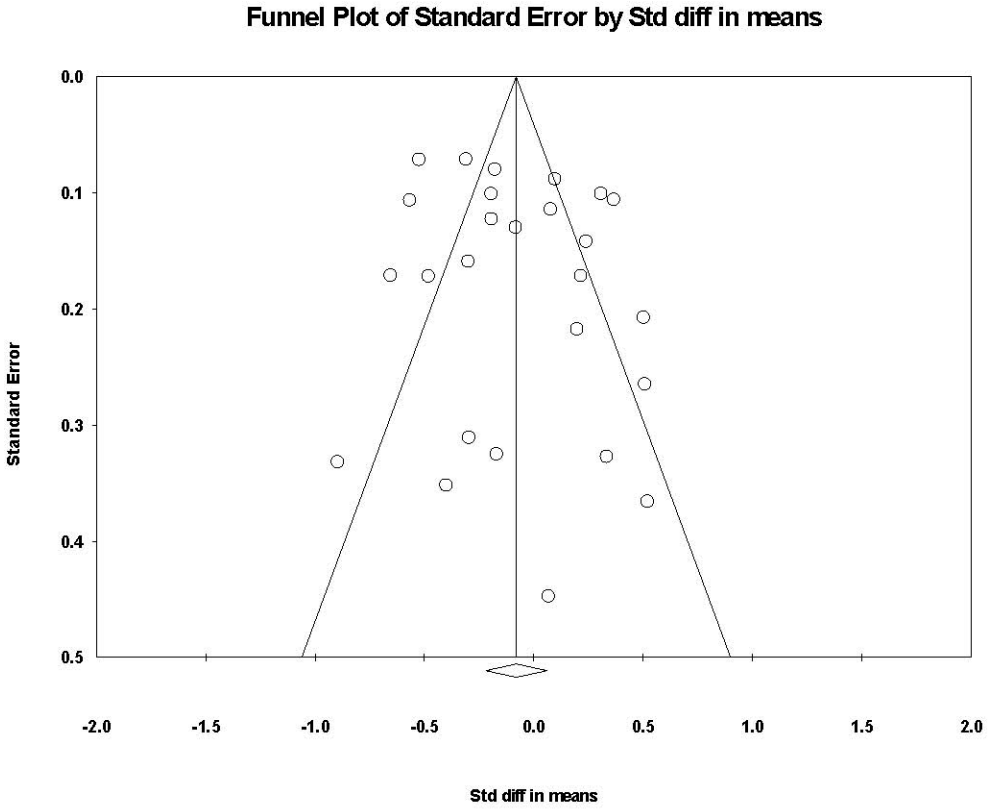
Appendix H. Analyses of Potential Publication Bias

We used Comprehensive Meta-Analysis Version 2 (Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis Version 2, Biostat, Englewood NJ [2005]) to test for potential publication bias for the outcomes described below.

Diastolic Blood Pressure Reduction

We used Comprehensive Meta-Analysis to examine any potential publication bias in the studies of diastolic blood pressure reduction. The resulting funnel plot is shown in Figure H1.

Figure H1. Funnel plot for studies of diastolic blood pressure reduction

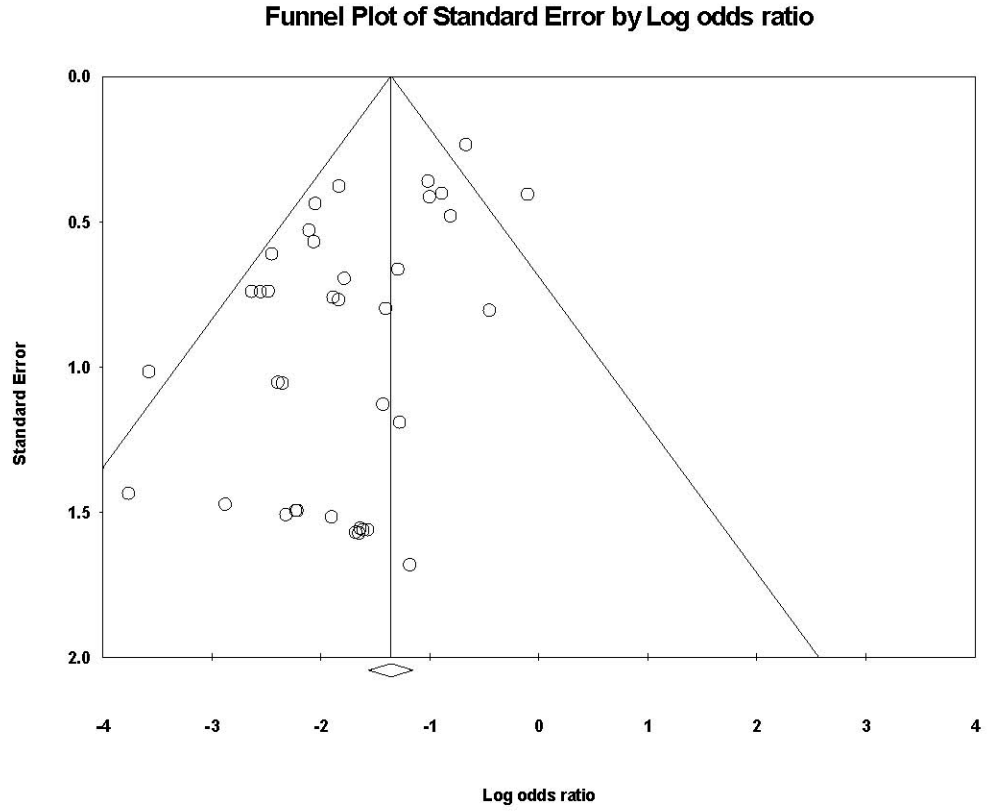


Note that there is no asymmetry in the plot. Six studies lie to the left of the funnel, and five or six studies lie to the right. The software computed Begg and Mazumdar's correlation test for publication bias. The correlation was 0.0369 (two-tailed p-value = 0.7914). Thus there was no evidence of publication bias in this meta-analysis.

Cough In Trials Studying Diastolic Blood Pressure Reduction

We used Comprehensive Meta-Analysis to examine any potential publication bias in the RCT studies of cough in trials studying blood pressure control. The funnel plot for the studies is shown in Figure H2.

Figure H2. Funnel plot for RCTs of cough in trials studying blood pressure control

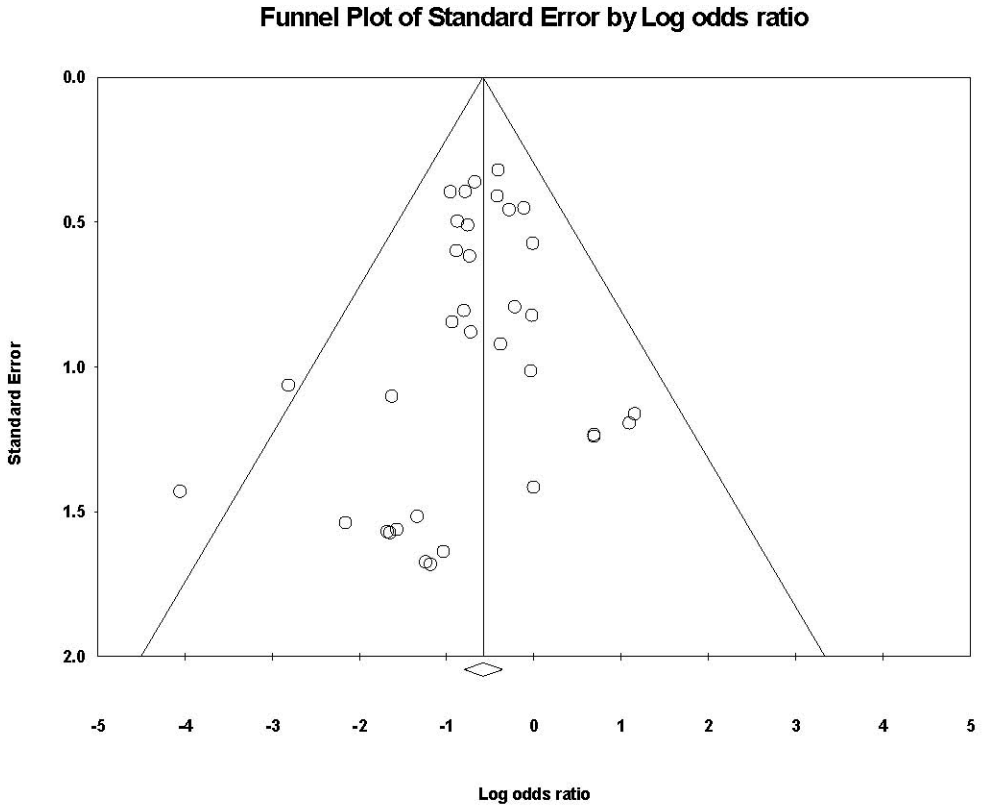


Note that there is no asymmetry in the plot. One of the studies lies to the left of the funnel and two of the studies lie to the right. The software computed Begg and Mazumdar's correlation test for publication bias. The correlation was 0.000 (two-tailed p-value = 1.000). Thus there was absolutely no evidence of a publication bias in this meta-analysis.

Withdrawals Due to Adverse Events

We used Comprehensive Meta-Analysis to examine any potential publication bias in studies reporting withdrawals due to adverse events. The funnel plot for the studies is shown in Figure H3.

Figure H3. Funnel plot for studies reporting withdrawals due to adverse events



Note that there is no asymmetry in the plot. Two of the studies lie to the left of the funnel, and none of the studies lies to the right. The software computed Begg and Mazumdar's correlation test for publication bias. The correlation was -0.1113 (two-tailed p-value = 0.3404). There is no evidence of a publication bias in this meta-analysis.