Comparative Effectiveness Review

Number 10

Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension

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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 State Children's Health Insurance Program (SCHIP).

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 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 Comparative Effectiveness Reviews 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.

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Background

More than 65 million American adults—approximately one-third—have hypertension. The prevalence of hypertension increases with advancing age such that more than half of people 60-69 years of age and approximately three-fourths of those 70 years of age and older are affected. In addition to being the number one 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 morbidity and mortality attributable to hypertension, control remains suboptimal. In addition to several effective nonpharmacological interventions—including diet, exercise, and control of body weight—many individuals will 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. The primary site of renin release is the kidney, and release is triggered by sympathetic stimulation, renal artery hypotension, and decreased sodium delivery to the distal tubule. Via 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; stimulates the adrenal cortex to release aldosterone, leading to increased sodium and water reabsorption and potassium excretion; promotes secretion of antidiuretic hormone, leading to fluid retention; stimulates thirst; promotes adrenergic function; and increases 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, therapies fall into one of two classes of angiotensin antagonists: the angiotensin-converting enzyme inhibitors (ACEIs) and the angiotensin II receptor antagonists (ARBs, or angiotensin receptor blockers). ACEIs block conversion of angiotensin I to angiotensin II. ARBs selectively inhibit angiotensin II from activating the angiotensin specific receptor (AT_1).

While ACEIs and ARBs both target the renin system and are regarded by clinicians as effectively equivalent, it is not clear that this is appropriate. ACEIs, for example, do not entirely block production of angiotensin II because of the presence of unaffected converting enzymes. Also, ACEIs are associated with well-known adverse events not shared by ARBs, including cough (estimated incidence 5-20 percent) and the possibly related phenomenon of angioedema

(estimated incidence 0.1-0.2 percent). It would be clinically useful to have a clear understanding of the state of the science with regard to the relative effectiveness of ACEIs and ARBs.

This review summarizes the evidence on the comparative long-term benefits and harms of ACEIs versus ARBs, focusing on their use for treating essential hypertension in adults. Key questions addressed are:

Key Question 1. For adult patients[a] with essential hypertension, how do ACEIs and ARBs[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 and ARBs differ in safety,[d] adverse events,[e] tolerability, persistence, and adherence?

Key Question 3. Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or 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 vs. ARBs for adults with essential hypertension.

[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®).

[c] Outcomes considered include:

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; measures of left ventricular (LV) mass/function; and measures of kidney disease.

Health outcomes—Mortality (all-cause mortality, cardiovascular disease-specific mortality, and cerebrovascular disease-specific mortality) and morbidity (cardiac events [myocardial infarction], heart failure, cerebral vascular disease or events [including stroke], symptomatic coronary artery disease, end stage renal disease, peripheral vascular disease, and quality of life).

[d] Safety outcomes considered were overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, and switch rates.

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

Table A. Summary of evidence on comparative long-term benefits and harms of ACEIs vs. ARBs for essential hypertension

Key question	Strength of evidence	Conclusions
Key Question 1. For adult patients with essential hypertension, how do ACEIs and ARBs differ in the following health outcomes:		
a. Blood pressure control	High	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 50 studies (47 RCTs, 1 nonrandomized controlled clinical trial, 1 retrospective cohort study, and 1 case-control study) in which 13,532 patients receiving an ACEI or an ARB were followed for periods from 12 weeks to 5 years (median 16.5 weeks). Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols.
b. Mortality and major cardiovascular events	Moderate	Due to insufficient numbers of deaths or major cardiovascular events in the included studies, it was not possible to discern any differential effect of ACEIs vs. ARBs for these critical outcomes. In 9 studies that reported mortality, MI, or clinical stroke as outcomes among 3,356 subjects, 16 deaths and 13 strokes were reported. This may reflect low event rates among otherwise healthy patients and relatively few studies with extended followup.
c. Quality of life	Low	No differences were found in measures of general quality of life; this is based on 4 studies, 2 of which did not provide quantitative data.
d. Rate of use of a single antihypertensive	High	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.
e. Risk factor reduction and other intermediate outcomes	Moderate (lipid levels, markers of carbohydrate metabolism/ diabetes control, progression of renal disease) to Low (progression to type 2 diabetes and LV mass/function)	There were no consistent differential effects of ACEIs vs. ARBs on several potentially important clinical outcomes, including lipid levels, progression to type 2 diabetes mellitus, markers of carbohydrate metabolism/diabetes control, measures of LV mass or function, and progression of renal disease (either based on creatinine, GFR, or proteinuria). Relatively few studies assessed these outcomes over the long term.

Table A. Summary of evidence on comparative long-term benefits and harms of ACEIs vs. ARBs for essential hypertension (continued)

Key question	Strength of evidence	Conclusions
Key Question 2. For adult patients with essential hypertension, how do ACEIs and ARBs differ in safety, adverse events, tolerability, persistence, and adherence?	High (cough, withdrawals due to adverse events) to Moderate (persistence/ adherence) to Low (angioedema)	ACEIs have been consistently shown to be associated with greater risk of cough than ARBs: pooled odds ratio (Peto) = 0.32. For RCTs, this translates to a difference in rates of cough of 6.7 percent (NNT = 15); however, for cohort studies with lower rates of cough, this translates to a difference of 1.1 percent (NNT = 87). This is generally consistent with evidence reviewed regarding withdrawals due to adverse events, in which the NNT is on the order of 27—that is, 1 more withdrawal per 27 patients treated with an ACEI vs. an ARB. There was no evidence of differences in rates of other commonly reported specific adverse events. Angioedema was reported only in patients treated with ACEIs; however, because angioedema was rarely explicitly reported in the included studies, it was not possible to estimate its frequency in this population. ACEIs and ARBs have similar rates of 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.
Key Question 3. Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?	Very low	Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs and ARBs for any particular patient subgroup.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker/antagonist; GFR = glomerular filtration rate; LV = left ventricular; MI = myocardial infarction; NNT = number needed to treat; RCT = randomized controlled trial.

Remaining Issues

Despite the relative importance of both ACEIs and ARBs for treatment of essential hypertension, there is a paucity of 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 data on adverse events are inconsistently reported. Only nine studies compared ACEIs and ARBs for periods longer than 1 year.

Future Research

With the exception of rates of cough, the hypothesis that ACEIs and ARBs 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 research in this area should consider:

- 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.

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.

Introduction

Background

More than 65 million American adults (one-third) have hypertension. The prevalence of hypertension increases with advancing age such that more than half of people 60 to 69 years of age and approximately three-fourths of those 70 years of age and older are affected.[1] Furthermore, increasing prevalence of obesity may further increase the prevalence of hypertension in the United States. According to estimates from the World Health Organization, worldwide prevalence estimates for hypertension may be as much as 1 billion individuals, and suboptimal blood pressure is the number one attributable risk factor for death throughout the world.[2] Substantial excess morbidity also occurs when hypertension affects numerous target organs including the brain, eyes, heart, arteries, and kidneys.

Despite the high morbidity and mortality attributable to hypertension, control remains suboptimal. Approximately one-third of adults remain unaware of their hypertension, over 40 percent of individuals with hypertension are not on treatment, and two-thirds of hypertensive patients continue to have blood pressures 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. Multi-drug therapy is often required to achieve satisfactory control, leading to greater variables to consider in treatment choices.[3] Finally, adverse events that are characteristic of the individual agents or drug classes further complicate therapeutic decisionmaking.

The renin-angiotensin-aldosterone (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. The primary site of renin release is the kidney, and release is triggered by sympathetic stimulation, renal artery hypotension, and decreased sodium delivery to the distal tubule. Via 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; stimulates the adrenal cortex to release aldosterone, leading to increased sodium and water reabsorption and potassium excretion; promotes secretion of antidiuretic hormone, leading to fluid retention; stimulates thirst; promotes adrenergic function; and increases 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.[4,5] Currently, therapies fall into one of two classes of angiotensin antagonists: the angiotensin-converting enzyme inhibitors (ACEIs), and the angiotensin II receptor antagonists (ARBs or angiotensin

receptor blockers). ACEIs block conversion of angiotensin I to angiotensin II. ARBs selectively inhibit angiotensin II from activating the angiotensin specific receptor (AT_1).

While ACEIs and ARBs both target the renin system and are regarded by clinicians as effectively equivalent, it is not clear that this is appropriate. ACEIs, for example, do not entirely block production of angiotensin II due to the presence of unaffected converting enzymes. Also, ACEIs are associated with well-known adverse events not shared by ARBs, including cough (estimated incidence 5 to 20 percent) and the possibly related phenomenon of angioedema (estimated incidence 0.1 to 0.2 percent).[6] Further, distinguishing effectiveness between these two groups of commonly used angiotensin antagonists is particularly problematic. Although both ACEIs and ARBs are highly effective in lowering blood pressure among patients with essential hypertension,[4,5] the comparative effectiveness of the ACEIs and ARBs is not known. In addition, because many patients with hypertension require multiple medications to achieve adequate blood pressure control, angiotensin antagonists are often optimal second-line antihypertensive drugs. However, the relative advantages and disadvantages of ACEIs versus ARBs are not well known despite several studies that have compared the effectiveness within other classes of antihypertensive drugs as well as recent drug class reviews for ACEIs[4] and ARBs.[5]

In this comparative effectiveness review, we examine the scientific literature on ACEIs and ARBs for individuals with hypertension regarding their relative benefits (blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes), as well as relative risks (safety, adverse events, tolerability, persistence, and adherence). In addition, we will examine the clinical determinants of these outcomes with a focus on the long-term impact.

Scope and Key Questions

This review summarizes the evidence on the comparative long-term benefits and harms of ACEIs versus ARBs 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) and ARBs (angiotensin II receptor antagonists)[b] differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes[c]?

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

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

[c] Outcomes considered include:

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; measures of left ventricular (LV) mass/function; and measures of kidney disease.

Health outcomes: Mortality (all-cause mortality, cardiovascular disease-specific mortality, and cerebrovascular disease-specific mortality); and morbidity (cardiac events [myocardial infarction], heart failure, cerebral vascular disease or events [including stroke], symptomatic coronary artery disease, end-stage renal disease, peripheral vascular disease, and quality of life).

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

Key Question 3. Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?

[d] Safety outcomes: 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, cough and angioedema.

Table 1. Characteristics and labeled indications of ACEIs and ARBs 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 m²) 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 and ARBs 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 then 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 and ARBs 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 m², 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 and ARBs 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 2 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 occurs within 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 death and heart failure.	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, ACEIs 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 and ARBs 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 and ARBs 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.

Abbreviations: 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 this report 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 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.

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 materials received from the SRC, the reference lists of relevant review articles, and citations identified by peer and public reviewers of the draft report. We did not undertake a systematic search for unpublished data.

To identify literature describing direct comparisons of ACEIs versus ARBs we searched:

- MEDLINE® (1966 to May Week 3 2006).
- The Cochrane Central Register of Controlled Trials.
- A register of systematic reviews underway in the Cochrane Hypertension Review Group.
- Scientific information packets submitted through the SRC by AstraZeneca, Bristol-Myers Squibb, Kos, and Merck.

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 this review. The search strategies used to identify this potentially relevant indirect comparator literature are included in Appendix A. The process used to screen this literature and evaluate its relevance is described in Appendix B.

Our searches identified a total of 1,185 citations. We imported all citations into an electronic database (ProCite® 4).

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 potentially relevant indirect comparator studies (ACEI versus non-ARB or placebo and ARB versus non-ACEI or placebo), as well as direct head-to-head comparator studies. We retrieved the full text of all potentially relevant abstracts for further review. In the case of direct comparator studies, we applied a second, more stringent set of criteria for inclusion and exclusion (Appendix C). Full-text screening of the indirect comparative literature proceeded along a separate track, which is described in Appendix B.

The remainder of this section describes in greater detail the criteria we used to screen the direct comparator 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 and ARBs listed in Table 1. In addition to straightforward comparisons of a single ACEI versus a single ARB, we also included "grouped" comparisons (e.g., a specific ARB versus "ACEIs" or unspecified "ARBs" versus 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 versus ARBs. These are listed above in the section on "Scope and Key Questions." In somewhat greater detail, and in order of relative priority, these outcomes were:

- 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 [MI, stroke] and measures of quality of life).

- Safety (focusing on serious adverse event rates, overall adverse event rates, and withdrawals due to adverse events).

- Specific adverse events (including, but not limited to, cough and angioedema).

- Persistence/adherence.

- Rate of use of a single antihypertensive for blood pressure control.

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

The key questions ask about the comparative *long-term* benefits and harms of ACEIs versus ARBs for treating essential hypertension, but do not define precisely what is meant by "long-term." We initially interpreted this to mean 6 months or longer, but decided after the abstract screening to reduce this to 12 weeks or longer. We made this decision for two reasons: (1) the distribution of length of followup was highly skewed toward shorter duration, so that a longer threshold would have excluded nearly all head-to-head studies of ACEIs and ARBs; (2) a strong differential benefit or harm detected in a short-duration study could be important to identify, especially if similar effects were suggested, perhaps less strongly, by longer-term studies.

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.

We excluded studies with fewer than 20 total patients in the ACEI and ARB treatment arms.

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 is provided in Appendix E.

We extracted the following data from included trials: 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 CRD.[7,8]

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:
   - For RCTs: Adequate randomization, including concealment and whether potential confounders were distributed equally among groups.
   - 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.[9] These criteria, slightly adapted by the SRC, 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.

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.

Rating the Body of Evidence

We assessed the strength of the body of evidence for each key question using the GRADE framework.[10] 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. In addition, as part of the GRADE framework, we assessed the consistency across studies of the same design, consistency across different study designs, the magnitude of effect, and applicability. Finally, if applicable, we considered the likelihood of publication bias and (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 – Further research is very unlikely to change our confidence in the estimate of effect.

Moderate – Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low – Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low – Any estimate of effect is very uncertain.

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 pooling 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 homogeneity. 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 test for heterogeneity and to pool (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 likely explanatory clinical and methodological study characteristics to determine whether they could explain the heterogeneity observed. If, after this further scrutiny, studies appeared to be clinically and methodologically similar, we performed pooling even in the presence of statistical heterogeneity. Pooled estimates combining both study designs were also calculated in order to estimate confidence limits for an overall effect.

When pooling 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 count outcomes, we calculated a summary of the relative effect (odds ratio) and absolute effect (risk difference). When the results from statistical testing were similar, we present the outcome that we judged to be most clinically relevant. We also present the

number-needed-to-treat (NNT) when effects are statistically significant. In calculating the NNT, we used either the inverse of the risk difference (when risk difference is presented as the pooling measure), or the inverse of an estimated difference based on an average control event rate and a relative measure of effect (when odds ratio is used as the measure for pooling).

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. Also, we did not specifically consider study design in deciding whether to pool, but when we did pool, we stratified the analysis to examine differences between observational studies and randomized controlled trials, as described above.

In deciding whether to pool indirect comparison studies, we adopted a similar approach. However, given the more tenuous nature of indirect comparisons, we used specific quantitative criteria for pooling (see Appendix B).

Results

Literature Search and Screening

Our searches of the literature identified a total of 1,185 citations. Table 2 details the number of citations identified from each source.

Table 2. Sources of citations

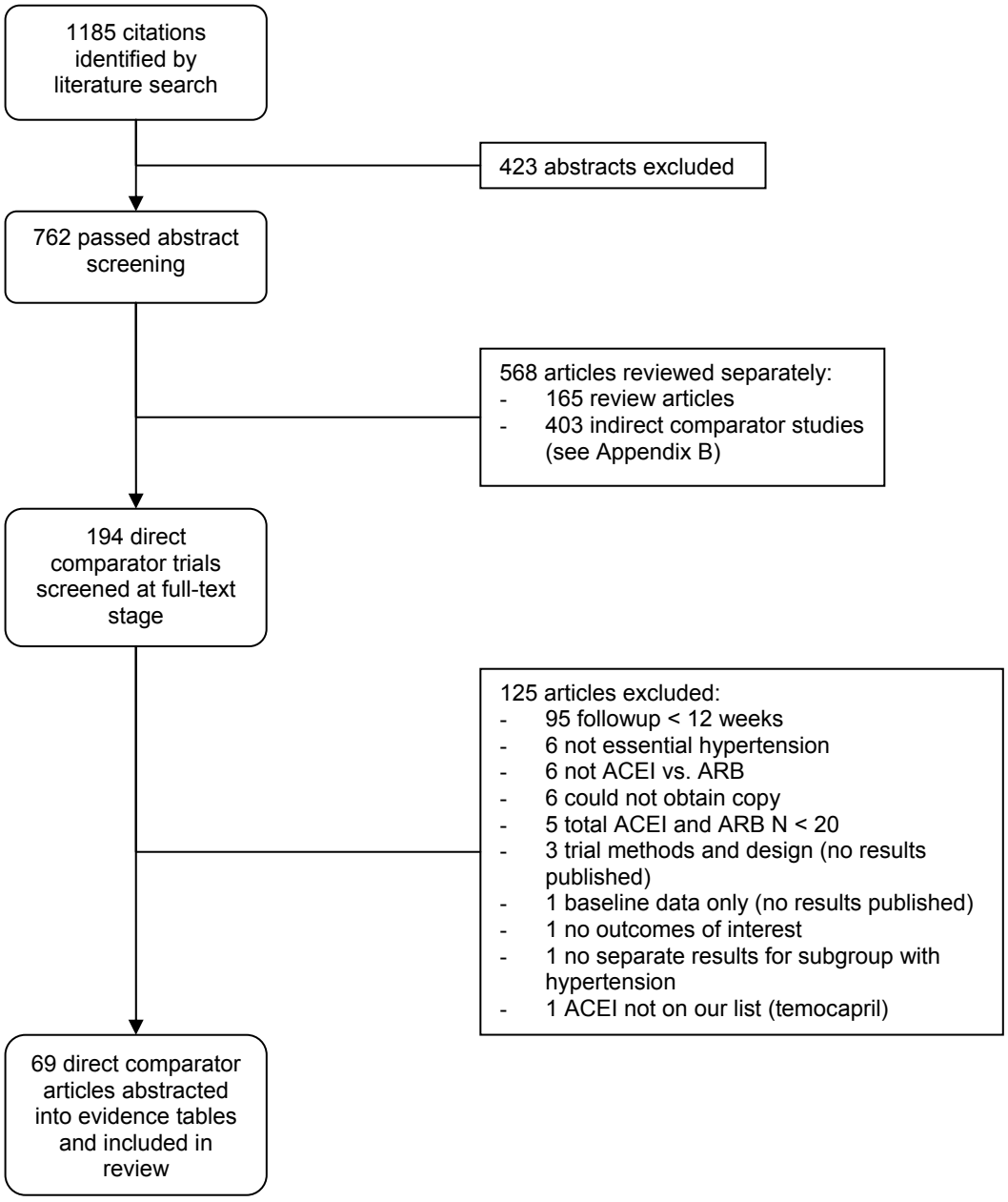
Source	Number of citations
MEDLINE®	1078
Cochrane Central Register of Controlled Trials	45
Register of systematic reviews underway in the Cochrane Hypertension Group	0
References of review articles and primary studies	23
Scientific information packets submitted by pharmaceutical companies	17
Other (recommendations from staff at AHRQ or SRC or from project investigators)	22
Total:	**1185**

Figure 1 describes the flow of literature through the screening process. Four hundred and twenty-three (423) citations were excluded at the abstract screening stage. Of the 762 citations that passed the abstract screening, 165 were review or methods articles, 136 were studies of ACEIs versus other (non-ARB) comparators, 267 were studies of ARBs versus other (non-ACEI) comparators, and 194 were direct comparator studies of ACEIs versus ARBs.

The remainder of this section describes results for the direct comparator studies. As stated above and described in Appendix B, we considered incorporating evidence from indirect studies for important outcomes that were under-reported in the direct comparator trials, but we were unable to identify a pool of comparable ACEI and ARB studies for this analysis.

At the full-text screening stage, 125 of the 194 direct comparator studies were excluded for the reasons summarized in Figure 1, leaving a total of 69 included articles. Appendix G provides a complete list of excluded head-to-head studies, with reasons for exclusion.

Figure 1. Literature flow diagram



The 69 included direct comparator articles reported on 61 distinct studies. Forty-seven (47) of these were RCTs, one was a nonrandomized controlled trial, nine were retrospective cohort studies, two were prospective cohort studies, and one study each was a cross-sectional cohort and a case-control study. Table 3 describes the number of studies that evaluated various possible treatment comparisons.

Table 3. Number of included studies (number of publications) that evaluated various treatment comparisons

ACEIs	ARBs								
	"ARBs"	**Candesartan cilexetil**	**Eprosartan**	**Irbesartan**	**Losartan**	**Olmesartan medoxomil**	**Telmisartan**	**Valsartan**	**Totals**
"ACEIs"	9 (11)	1 (1)	0	2 (2)	2 (2)	0	0	0	14 (16)
Benazepril	0	0	0	0	0	0	0	0	0
Captopril	0	0	0	0	2 (2)	0	0	0	2 (2)
Enalapril	0	4 (4)	2 (6)	4 (4)	10 (12)	0	3 (3)	1 (1)	24 (30)
Fosinopril	0	0	0	2 (2)	1 (1)	0	0	0	3 (3)
Lisinopril	0	4 (4)	0	0	0	0	1 (1)	3 (3)	8 (8)
Moexipril	0	0	0	0	0	0	0	0	0
Perindopril	0	1 (1)	0	0	1 (1)	0	2 (2)	0	4 (4)
Quinapril	0	0	0	0	2 (2)	0	0	0	2 (2)
Ramipril	0	0	0	0	0	0	3 (3)	0	3 (3)
Trandolapril	0	0	0	0	1 (1)	0	0	0	1 (1)
Totals:	9 (11)	10 (10)	2 (6)	8 (8)	19 (21)	0	9 (9)	4 (4)	-

As Table 3 illustrates, enalapril was by far the most frequently studied ACEI (24 studies) and losartan the most frequently studied ARB (19 studies), followed by candesartan cilexetil (10 studies). The most commonly studied treatment comparison was enalapril versus losartan (10 studies), followed by the more generic "ACEIs" versus "ARBs" (9 studies). Other treatment comparisons were fairly sparsely represented.

In terms of quality, 39 studies were rated as fair, 17 as poor, and 5 as good. The distribution of studies by followup time is given in Table 4.

Table 4. Distribution of included studies by followup time

Treatment duration/followup time	Number of studies
12 weeks	19
14-16 weeks/3-4 months	8
24-26 weeks/6 months	13
10-11 months	2
48 weeks	3
1 year	7
15 months	1
720 days	1
3 years	3
39 months	1
4 years	2
5 years	1

There was no obvious correlation between study quality and length of followup. The five good-quality studies varied in length from 12 weeks (2 studies) to 16 weeks (1 study) to 1 year (2 studies).

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

Key Points

- There was no clear difference in the blood pressure lowering efficacy between ACEIs and ARBs.
- Few deaths or major cardiovascular events occurred in the identified studies comparing ACEIs to ARBs; this precluded any assessment of a differential effect of ACEIs and ARBs on these events.

- No significant difference was observed between ACEIs and ARBs in terms of their impact on quality of life.

- There was no statistically evident difference in rate of treatment success based on use of a single antihypertensive for ARBs compared to ACEIs.

- Available evidence suggests that ACEIs and ARBs have a similar lack of impact on lipid levels for individuals with essential hypertension.

- Available evidence suggests that ACEIs and ARBs have a similar lack of impact on glucose levels or HgbA1c for individuals with essential hypertension.

- Evidence does not demonstrate a difference between ACEIs and ARBs with regard to their effect on 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 GFR with use of ACEIs versus ARBs.

- 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 versus ARBs.

Effect on Blood Pressure

Fifty (50) studies described in 56 separate publications met our inclusion criteria and reported a blood pressure outcome. Of these, five (10 percent) were of good methodological quality,[11-15] 32 (64 percent; 37 papers) were of fair quality,[16-52] and 13 (26 percent; 14 papers) were of poor quality.[53-66] There was one nonrandomized controlled clinical trial,[65] one retrospective cohort study,[19] and one case-control study;[63] the remaining 47 studies were RCTs. Sample sizes for individual studies ranged from 29 to 2416 patients, with a total of 16,597 patients (13,532 of whom received an ACEI or an ARB). Study durations ranged from 12 weeks to 5 years, with a median of 16.5 weeks.

The mean age of study participants ranged from 38 years to 73 years, with a median of 54.1 years. The proportion of female patients included ranged from 19 to 100 percent, with a median of 47 percent. Only 25 studies (50 percent; 30 papers) reported the racial demographics of the study participants.[12-16,18,23-25,27-32,34,35,38,41,42,44-49,52,56,59,65] Of these 25 studies, only nine (36 percent; 13 papers) enrolled a minimum of 10 percent of ethnic minority participants.[15,24,27-32,34,35,44,47,49] Seven of the included studies (14 percent; 11 papers) were conducted in part or entirely within the United States,[15,24,27-32,34,35,49] with the remainder carried out in other countries. The funding source was reported in only 28 studies (56 percent; 33 papers),[12-17,19,21-23,27-31,34,36-38,41,44,47-53,56,61-63,65] with the majority of these (23 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 141 to 181 mm Hg and 84 to 119 mm Hg, respectively, with a mean starting blood pressure of 158.8/98.6 mm Hg. There was significant heterogeneity in the study protocols and data reporting. Fewer than half of the studies (22/50; 44 percent; 23 papers) did

not allow additional hypertension medications during the study;[11,18,22,24,25,33,34,36,38,40-43,45-48,50,51,56,59,65,66] 18 studies (36 percent; 22 papers) allowed additional medications according to a specified protocol;[12,14-17,20,23,27-32,35,37,39,44,49,54,60,63,64] five studies (10 percent; 6 papers) allowed additional medications at the discretion of the treating physician;[13,19,21,52,61,62] and five studies (10 percent) did not report concomitant hypertension therapy.[26,53,55,57,58] The reported blood pressure endpoints varied as well, with 13/50 studies (26 percent; 14 papers) reporting mean change in blood pressure and final posttreatment blood pressure;[14,15,24,26,32,33,38,40,41,44-47,59] 19 studies (39 percent; 20 papers) reporting only final posttreatment blood pressure;[12,16-18,20,22,23,43,51,53-56,58,60-65] 15 studies (30 percent; 19 papers) reporting only mean change in blood pressure in each study arm;[11,13,19,21,25,27-31,34,35,39,42,48-50,52,66] and three studies (6 percent) not providing quantitative data for the blood pressure outcome or reporting only the proportion of patients achieving a target blood pressure.[36,37,57]

For the overall comparison of blood pressure lowering between ACEIs and ARBs, 37 studies reported no difference (74 percent; 42 papers),[11-14,16-18,21-23,26-32,34-41,43,44,49,51-58,60-65] two studies favored ACEIs (4 percent; 3 papers),[15,45,46] eight studies favored ARBs (16 percent),[24,25,33,42,47,48,50,59] and three studies (6 percent) did not report the comparison between the two agents.[19,20,66] 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.

Effect on Mortality and Major Cardiovascular Events

The literature review identified 13 publications[12-14,23,25,27-31,51,52,60] describing nine separate studies that reported patient mortality, MI, or clinical stroke as outcomes. All nine studies were RCTs. They included 3356 patients (3322 of whom received an ACEI or an ARB) and ranged in duration from 12 weeks to 5 years, and most reported blood pressure measurements as primary endpoints. The treatment comparisons studied were: candesartan versus enalapril, eprosartan versus enalapril, losartan versus enalapril, losartan versus fosinopril, telmisartan versus ramipril, telmisartan versus enalapril, and valsartan versus lisinopril.

In general the studies were of fair quality. Notably, the majority of studies in this review – including those reporting morality and major cardiovascular events – excluded patients with significant cardiovascular disease and often other comorbid conditions.

The included studies shed little light on the issue of relative rates of mortality, MI, or stroke with ACEIs versus ARBs. In nine studies involving 3356 patients, 16 patients died. The study by Barnett et al.[52] 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, six in the telmisartan group (three due to stroke, MI, and heart failure), and six in the enalapril group (two due to MI).

Among shorter-term trials, the study by Ruilope et al.,[13] 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.[51] 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.[27] is the primary report of a trial of eprosartan versus enalapril over 26 weeks. A substudy from this trial published by Gavras et al.[29] reported that one patient assigned to the eprosartan group had an anteroseptal MI and died. Finally, Williams et al.[25] evaluated telmisartan versus ramipril over 14 weeks and reported that one patient in the ramipril group had a stroke. In none of these trials did investigators attribute any of the events observed directly to therapy.

Given the importance of this long-term outcome and the absence of significant data on major cardiovascular events, we turned to the indirect evidence (i.e., comparing an ACEI and an ARB to a common comparator, but not to each other.) However, this evidence was not deemed suitable for any indirect comparison (see Appendix B). In particular, a key risk factor for major events – namely, mean subject age – was widely discrepant in the small pool of potential indirect studies.

Effect on Quality of Life

Four studies described in eight separate papers met our inclusion criteria and reported quality of life.[27-31,39,43,50] All four were RCTs and 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.[39,50]

Sample sizes for the individual studies ranged from 42 to 528 patients, with a total of 1142 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;[27] 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;[27,50] two administered the Subjective Symptoms Assessment profile;[27,43] one study employed the MacMaster Overall Treatment Evaluation Questionnaire;[50] and one used the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36).[39] 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.[27,43]

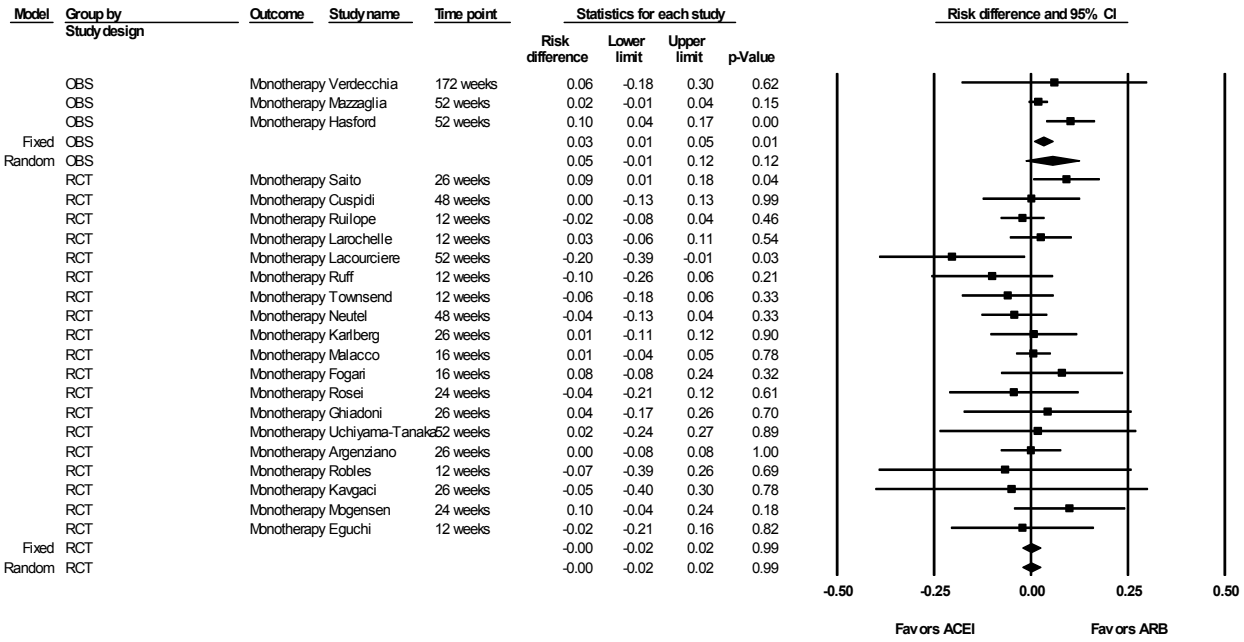
None of the studies found any difference between ACEIs and ARBs in their impact on the quality of life of study participants; indeed, no study demonstrated an impact on quality of life for subjects treated with ACEIs *or* ARBs.

Effect on Rate of Use of a Single Antihypertensive Agent

We identified 22 studies that reported the outcome of successful monotherapy with an ACEI or ARB.[13-21,23,28,32,33,35,37,39,49,54,60,63,64,67] 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. Three of these studies were determined to be good quality, 15 were fair in quality, and four were poor. There were 19 RCTs, two retrospective cohorts, and one case-control study. Sample sizes ranged from 30 to 13,303 patients, with a total of 21,562 patients (12,010 of whom received an ACEI or ARB). 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 61 percent). The average proportion for successful monotherapy across all studies was 55.9 percent for both ACEIs and ARBs.

We performed a meta-analysis of data from the 22 studies (Figure 2). 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 ($Q = 25.8$; $I^2 = 18$ percent; d.f. = 21; $p = 0.22$). A summary estimate of the difference in the proportion of patients with successful blood pressure control on a single agent was 1.3 percent (95 percent CI -1.0 to 3.5 percent; $p = 0.26$; random-effects model; results based on odds ratios and median incidence were similar). 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. The trend favoring ARBs for this outcome appeared to be driven primarily by differences in tolerability and adherence, since the benefit of ARBs 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.

Figure 2. Successful monotherapy with ACEIs vs. ARBs



Effect on Lipid Levels

Twelve studies described in 17 papers met our inclusion criteria and evaluated lipid changes. Eleven of the 12 studies were RCTs;[11,12,17,18,23,26,27,40,45,60,64] one was an observational case-control study.[63] The ACEI-versus-ARB treatment comparisons were unique in nine studies and similar (losartan versus enalapril) in three.[23,45,63] Study periods ranged from 3 to 12 months, all of which were sufficiently long to detect measurable changes in the lipid profile.

Most of the 12 studies were fair in quality and none addressed the use of lipid-lowering agents during the study period. The two studies rated as good in quality[11,12] were moderately sized (70 and 96), 1-year investigations of Europeans with diabetes; however, they differed in mean age, proportion of females, recruitment settings, and time of onset of diabetes.

The majority of the available head-to-head evidence suggests that ACEIs and ARBs have a similar lack of impact on lipid parameters. Six studies directly compared outcomes between ACEI and ARB groups.[11,17,26,40,45,63] One study reported a decrease in LDL that was statistically greater in the ACEI group (perindopril -14 percent versus candesartan -4 percent),[11] and one reported a statistically significant greater percentage of individuals with an increase in LDL in the enalapril group than in the candesartan group (19.3 percent versus 11.5 percent).[17] Thus, for the two studies for which a difference was found, the difference was discrepant (i.e., an increase in LDL in one and a decline in LDL in the other). The remaining four studies that analyzed differences in outcomes between the two groups did not find a difference.

Nine studies found no change in total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), or triglyceride (TG) levels during the study period. The remaining three studies detected a small but statistically significant change in TC (two studies[23,60]), LDL (one study[11]), and TG (one study[60]) (Table 5). The magnitude of these changes was equivalent

for the compared medications except for one of the TC studies (ARB favored)[60] and the LDL study (ACEI favored).[11] Of these, only one was rated as good in quality.[11]

Table 5. Studies reporting significant changes in lipid profiles with ACEIs and/or ARBs

Study	N	Population	Quality	Comparators	ΔTC	ΔLDL	ΔHDL	ΔTG
Lacourciere et al.[23]	103	- Mean age 58 - 96% white - Canada - Diabetes	Fair	Losartan vs. enalapril	-2.1% vs. +4.2%*	NR	NR	NR
Derosa et al.[11]	96	- Mean age 54 - 100% white - Europe - Diabetes	Good	Candesartan vs. perindopril	NR	-4% vs. -14%*	+2% vs. -2%	+2% vs. -22%
Kavgaci et al.[60]	33	- Mean age 53 - 100% white - Turkey - Diabetes	Poor	Losartan vs. fosinopril	+0.01% vs. -0.1%*	NR	NR	-0.23%* vs. -0.21%*

*Statistically significant change (baseline to followup)
Abbreviations: HDL = low-density lipoprotein; LDL = low-density lipoprotein; N = number of subjects; NR=not reported; TC = total cholesterol; TG = triglyceride

The study by Schram et al.,[12] a broad-based community study comparing candesartan to lisinopril, found no change in lipid levels, while the study by Derosa et al.[11] comparing candesartan to perindopril in newly diagnosed diabetics attending a university-based internal medicine outpatient clinic found an improvement in LDL (favoring perindopril, -14 percent versus -4 percent), but no change in other lipid parameters. The broader population of the first study makes it more generalizeable; however, it allowed the sequential addition of specified antihypertensives to achieve a goal blood pressure. This heterogeneity in medication use makes attributing the outcomes to any single agent difficult. Both studies are limited by a failure to include races other than Caucasians. There were two large studies, one of 407[45] and one of 528 subjects.[27] Both were rated as fair in quality and neither detected a change in lipid parameters.

Effect on Markers of Carbohydrate Metabolism/Diabetes Control

Thirteen studies described in 18 papers met our inclusion criteria and measured glucose or HgbA1c. All but two[63,65] were RCTs. Overall, only two studies were rated as good in quality;[11,12] the remainder were rated as either fair (seven studies[18,21,23,26,27,40,45]) or poor (four studies[60,63-65]). The ACEI-versus-ARB comparisons tested were unique in seven studies; of the remaining six studies, enalapril and losartan were compared in four,[23,45,63,65] and candesartan and lisinopril in two.[12,21]

It is relevant that none of the 13 studies measuring glucose or HgbA1c changes addressed hypoglycemic therapy during the study period, and only six were specifically performed in diabetic populations.[11,12,21,23,40,60] Of the other seven studies, three permitted controlled diabetic patients but did not describe their proportion in the cohort;[27,45,63] one permitted diabetic subjects,

but they were in the minority (26 percent of subjects);[18] and three specifically excluded individuals with diabetes.[26,64,65]

The majority of the available head-to-head evidence suggests that ACEIs and ARBs have a similar lack of impact on glucose levels or HgbA1c. Six studies directly compared outcomes between the ACEI and ARB groups.[11,26,40,45,63,65] One study reported a small decrease in glucose that was statistically greater in the ACEI group (perindopril -15 ± 4 mg/dL, candesartan -8 ± 2 mg/dL),[11] and one reported a significant increase in HgbA1c (+0.25 percent enalapril versus +0.6 percent losartan) but did not directly compare the two groups.[23] Of these two studies only the former[11] was rated as good in quality. The other five studies that analyzed differences in outcomes between the two groups did not find a difference. Eleven studies compared baseline to followup glucose levels or HgbA1c and found no change for either the ACEI or ARB groups.

Effect on Measures of LV Mass or Function

Eight studies presented results on left ventricular (LV) mass or function assessed either by LV mass index (LVMI; 3 studies),[43,63,65] LV ejection fraction (LVEF; 2 studies),[53,58] or both (3 studies).[37,51,56] Table 6 summarizes relevant characteristics of all eight studies. Half of these studies had fewer than 50 patients,[43,51,53,65] while the other half had 100 or more patients.[37,56,58,63] All but two studies[63,65] were RCTs. Only two studies had relatively long-term followup (≥ 3 years);[43,63] however, the majority of studies had between 6 and 12 months of followup,[37,51,56,58,65] while one study had only 3 months of followup.[53] Because duration of therapy may significantly impact the ability to observe changes in LV mass or LV function, negative results must be interpreted with caution in studies with short-term followup.

Table 6. Characteristics of studies reporting LV mass/function outcomes

Study	Agents studied	Population	Design and size*	Duration	Quality	Outcome	Result
Cuspidi et al.[37]	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
Schieffer et al.[53]	Irbesartan vs. enalapril	CAD (? %LVH)	RCT N = 60 (48)	3 mo	Poor	LVEF	No difference No detailed data by treatment group
Avanza et al.[65]	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.[43]	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.[51]	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

Table 6. Characteristics of studies reporting LV mass/function outcomes (continued)

Study	Agents studied	Population	Design and size*	Duration	Quality	Outcome	Result
Verdecchia et al.[63]	Losartan vs. enalapril	LVH (23-24%)	Case-control N = 88	3.3 yr	Poor	LVMI	↓LVMI both, no difference between agents
Rajzer et al.[56]	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
Celik et al.[58]	Telmisartan vs. ramipril	HTN (? %LVH)	RCT N = 100	6 mo	Poor	LVEF	No change in LVEF in either group

* Size of study includes total enrolled, with followup population (if different) in parentheses.
Abbreviations: 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 eight studies identified did not demonstrate a difference between ACEIs and ARBs with regard to LV mass or function for individuals with essential hypertension. Six studies reported detailed data by treatment groups,[37,43,51,58,63,65] while one reported summary data,[56] and one described changes without presenting any data.[53] In general, the quality ratings of these studies describing changes in LV mass or function was poor. None was rated as being a good-quality study, and the majority (n = 5) were assessed to be of poor quality.[53,56,58,63,65] Various ARBs and ACEIs were studied, including five studies with losartan[43,51,56,63,65] and six studies with enalapril.[37,43,51,53,63,65] Among the six studies that presented detailed data on outcomes, three assessed LVMI,[43,63,65] one assessed LVEF,[58] and two assessed both LVMI and LVEF.[37,51]

The best and largest (n = 196) comparative study (an RCT) assessed LVMI and LVEF at baseline and after 48 weeks of followup.[37] The authors reported similar decreases in mean LVMI in both groups in both intention-to-treat and per-protocol analyses (36.3 percent on candesartan with normalized LVMI versus 28.6 percent on enalapril). No significant changes were observed for LVEF. 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.[43] Two non-randomized studies reported similar decreases in LVMI,[63,65] with one[65] demonstrating additional benefit in LVMI reduction with combination ACEI and ARB therapy. Only one study demonstrated a difference between groups for reduction in LVMI,[51] with lower reduction among those treated with losartan versus enalapril (24.7 ± 3.2 percent versus 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[37,51,63,65] or no change.[43,56] Reductions in LVMI appear to have occurred particularly among patients with established LV hypertrophy.[37,43,51,65] 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 and ARBs to improve or stabilize LVMI in patients with essential hypertension.

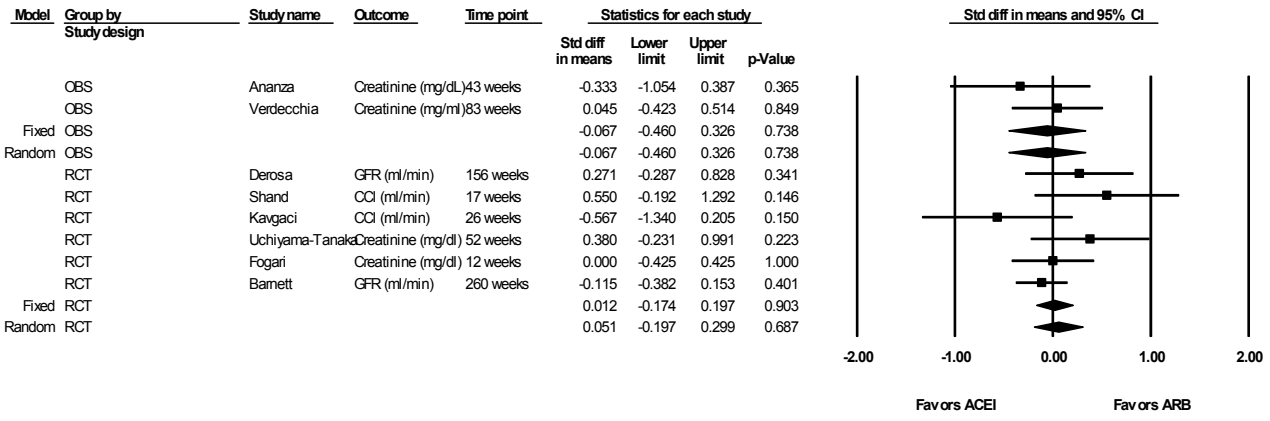
Effect on Serum Creatinine/GFR and Proteinuria

Review of the literature on the relative effects of ACEIs and ARBs on changes in renal intermediate outcomes identified 20 studies described in 26 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.[51] 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 19 studies, nine assessed either serum creatinine or GFR;[18,27,36,40,43,48,61,63,65] four assessed proteinuria;[11,12,21,68] and six assessed both.[17,23,45,52,55,60] Most studies included fewer than 100 patients; however, six had approximately 200 patients or more.[21,27,36,45,48,52] All but three[63,65,68] were RCTs. One study[52] 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.[36,40,45,61]

The 15 studies that described changes in creatinine or GFR did not consistently demonstrate differential effects related to renal function with use of ACEIs versus ARBs. Nine of these studies reported detailed data by treatment groups,[18,36,40,43,52,60,61,63,65] while two reported summary data,[23,45] and four described the changes without presenting any quantitative data.[17,27,48,55] Among the nine studies that reported data on renal function, none was rated as being a good-quality study; four were of poor quality;[60,61,63,65] two were nonrandomized studies;[63,65] and only two had more than 100 patients.[36,52] All but two[36,52] compared losartan with a specific ACEI; the ACEI most frequently studied was enalapril.[43,52,61,63,65]

The best comparative study assessed GFR by renal scintigraphy at baseline and after 3 years of followup.[43] 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 percent CI 0 to 0.06]) compared with the irbesartan group (change 0.01 mg/dL [95 percent CI -0.02 to 0.04]).[36] Nonetheless, serum creatinine remained unchanged before and after treatment in the other studies that reported detailed data for this outcome (Figure 3).

Figure 3. Studies evaluating renal function for ACEIs vs. ARBs

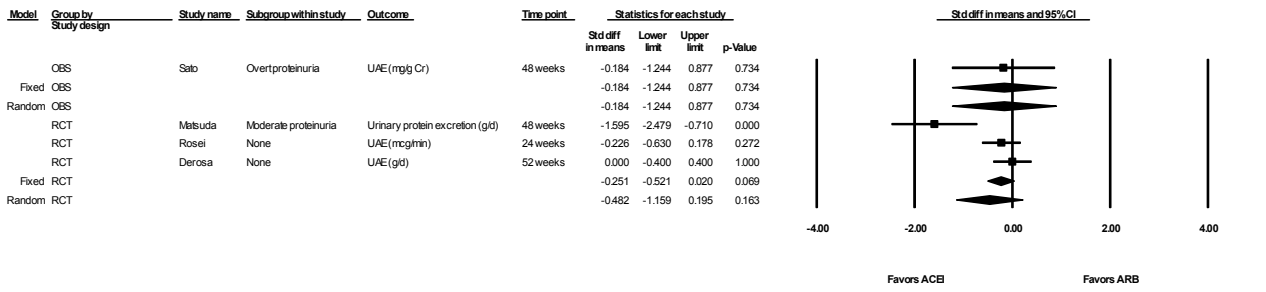


Key to Figure 3: CCl = creatinine clearance; GFR = glomerular filtration rate

Of two poor-quality studies that reported on changes in creatinine clearance, one reported no change.[61] Although the other study reported significant and similar decreases in creatinine clearance in both groups,[60] 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 nine percent mean decline in GFR assessed by radio-labeled excretion in each group ($p < 0.001$ at 52 weeks),[23] while the other found no change in mean percent change in serum creatinine.[45] Of the four studies that did not present data, two reported that there were no overall differences between groups;[17,55] another that the degree and direction of insignificant change in renal function were comparable in both treatment groups;[27] and the last described that 2 out of 192 patients treated with losartan developed an increase in serum creatinine during the 12-week study.[48]

The 10 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, nine of 10 studies reported detailed data by treatment groups, while one reported summary data in graphical format.[12] Among the nine studies that reported data, one was rated as being a good-quality study,[11] three were of poor quality;[55,60,68] one was a nonrandomized cohort study;[68] and only three had more than 100 patients.[21,45,52] Various ARBs were used, including one study with telmisartan,[52] four studies with candesartan,[11,17,21,68] three with losartan,[23,45,60] and one with both candesartan and losartan.[55] All studies assessed urinary albumin excretion except for one study that assessed urinary protein excretion.[55] Studies also varied in length of followup, with only one long-term study (5 years);[52] the remainder ranged from 12 weeks to 1 year. 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 (demonstrated graphically for the four studies that could be included in the meta-analysis in Figure 4).

Figure 4. Studies evaluating urinary protein excretion for ACEIs vs. ARBs



Key to Figure 4: UAE = urinary albumin excretion

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.[55] 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 ($p > 0.5$). The five studies that reported data in a format that could not be included in the meta-analysis also failed to demonstrate a differential effect.[21,23,45,52,60] 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 and ARBs differ in safety, adverse events, tolerability, persistence, and adherence?

Key Points

- Cough was modestly more frequently observed as an adverse event in groups treated with ACEIs than in groups treated with ARBs.
- Withdrawals due to adverse events were modestly more frequent for groups receiving an ACEI rather than an ARB; 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 reported only in patients treated with ACEIs; however, because angioedema was rarely explicitly reported in the included studies, it was not possible to estimate its frequency in this population.

- Adherence – in terms of pill counts in RCTs – is similarly high with both ACEIs and ARBs. However, persistence is generally lower with ACEIs, which appears to be explained largely by withdrawals due to cough (as above).

Safety and Adverse Events

Rates of serious and overall adverse events

Seven studies met our inclusion criteria and reported overall rates of serious adverse events.[14,17,24,25,36,39,48] One of these studies was rated as good in methodological quality, and the remaining six were fair. 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, was reported in only 3 of the 61 included studies (Table 7).[32,39,41] All of the reported cases occurred in patients treated with an ACEI. We did not pool these studies for two reasons. First, if we restricted pooling to the 3 studies, this did not meet our criterion for the minimal number of studies in a pool (n = 4). Second, if we included all 61 studies, it was not clearly valid to infer that there were no events simply because the study 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 7. Studies reporting angioedema

Study	Study design (blinding)	Interventions (numbers of patients)	Duration	Quality	Results
Karlberg et al.[39]	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.[41]	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.[32]	RCT (double-blinded)	Telmisartan (n = 385) Lisinopril (n = 193)	48 weeks	Fair	No cases of angioedema with telmisartan 2 cases with lisinopril

Of the 29 studies that met inclusion criteria and reported overall adverse event rates,[11,13-15,17,24,25,27,32-39,41,42,45,47-50,52,54,57,59,61,66] most were assessed as being fair (20 studies) or poor (five studies) in quality, and there was significant variation in the manner in which adverse events were reported. Depending on the definition used, adverse event rates ranged from 0 to 100 percent (median 32 percent) for ACEIs, and 0 to 96 percent (median 28 percent) for ARBs. Thus, data on overall rates of adverse events were not considered further.

Specific adverse events

Thirty studies reported rates of one or more specific adverse events,[11,13-15,23-25,27,32-39,41-45,47-50,57,59,68-70] including cough (29 studies), headache (21 studies), dizziness (18 studies), fatigue (10 studies), upper respiratory infection (6 studies), and nausea (6 studies). Viral infection, ankle edema, and back pain were reported as adverse events by three studies each. Palpitations, myalgia, diarrhea, malaise, and hypotension were reported by two studies each. Accident/injury, pharyngitis, rhinitis, dyspnea, abdominal pain, abnormal taste, urinary tract infection, constipation, dry mouth, feeling sick, pyrosis, insomnia, fever, asthenia, impotence, dyspepsia, musculoskeletal pain, flatulence, epigastric discomfort, increased sweating, erythematous rash, rhinitis, sinusitis, vertigo, flushing, cold hands/feet, 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.

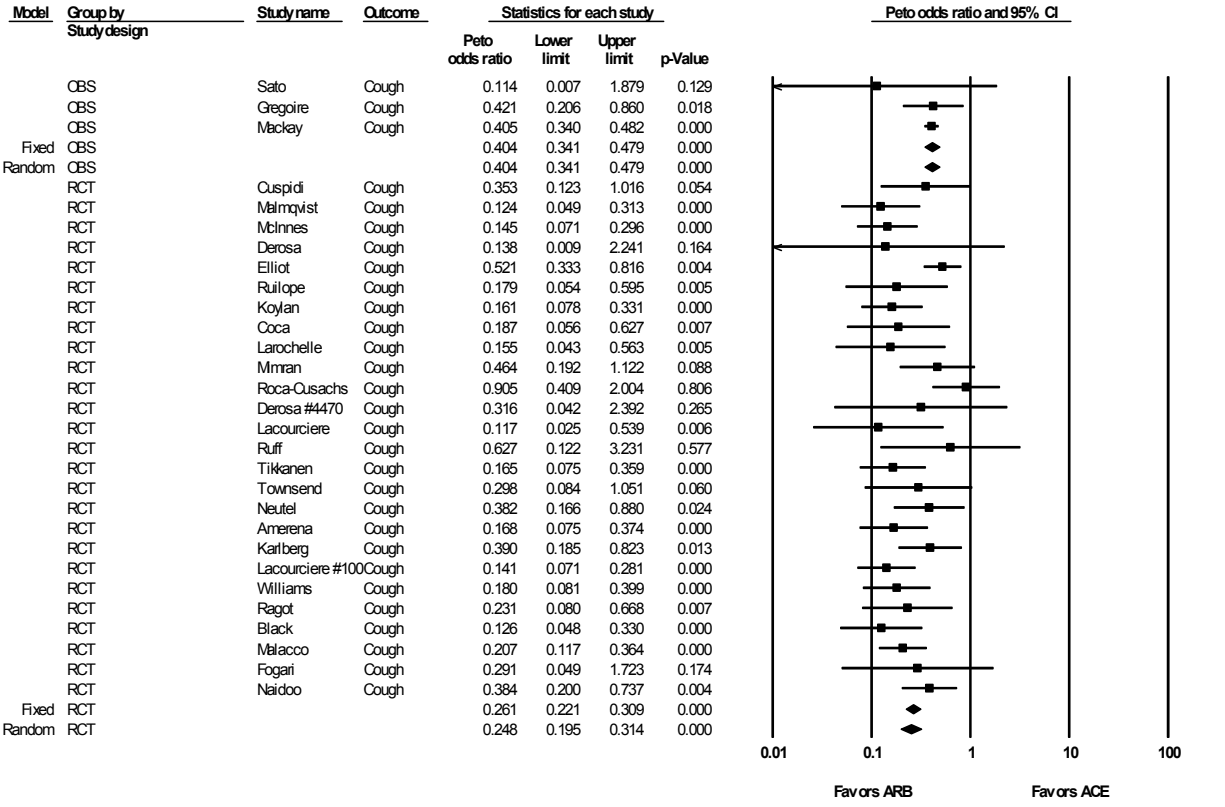
Given the large number of commonly reported specific adverse events, we focused on three specific events with the largest difference in absolute rates across studies: dizziness, headache, and cough. Rates of dizziness in studies reporting this event (n = 18) ranged from 1 to 20 percent in ARB-treated groups (mean 6 percent, median 4 percent) and from 0 to 18 percent in ACEI-treated groups (mean 7 percent, median 5 percent). For headache (n = 21 studies), rates ranged from 1 to 22 percent in ARB-treated groups (mean 8 percent, median 7 percent) and from 0 to 34 percent in ACEI-treated groups (mean 10 percent, median 7 percent). Our analysis of these figures showed no significant differences between ACEIs and ARBs (risk difference for dizziness 0.1 percent in favor of ACEIs, $p = 0.805$, fixed-effect model; risk difference for headache 0.7 percent in favor of ARBs, $p = 0.069$, fixed-effect model). These results suggest that there is no differential impact of ACEIs and ARBs with regard to dizziness or headache.

The one adverse event for which significant differential effects were apparent is cough. Twenty-nine studies compared cough in subjects treated with ACEIs and ARBs. In terms of quality, four were rated as good, 20 as fair, and five as poor. Of the 29 studies, 26 were RCTs, two were prospective cohort studies, and one was a cross-sectional cohort study. Sample sizes for the studies ranged from 49 to 51,410 patients, with a total of 61,978 patients. Study durations ranged from 12 weeks to 3 years, with a median of 16 weeks. The mean patient age of study participants was 57 years (standard deviation [SD] 6.25). The proportion of female patients included ranged from 19 to 100 percent. Eighteen studies (62 percent) reported the racial demographics of the study participants. Of these 18 studies, eight (44 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 3 percent, median 1 percent) and from 0 to 23 percent in ACEI-treated groups (mean 10 percent, median 9 percent). All 29 studies demonstrated higher rates of cough in ACEI-treated participants. For the meta-analysis of studies reporting cough as an adverse event, we included all studies that reported on cough rates (Figure 5). The Q test and the I^2 between studies demonstrated significant heterogeneity among the studies ($Q = 57.5$; $I^2 = 51.3$ percent). Performing a meta-analysis using a random-effects model leads to an estimated odds ratio (Peto) of 0.32 in favor of ARBs (95 percent CI 0.29 to 0.36; $p = 0.000$). Notably, the observed rates of cough appear much higher in RCTs than cohort studies; this is due to the higher detection when the patient is queried systematically for this symptom. Thus, based on the overall odds ratio of 0.32, when we use the rate of cough with ACEIs equal to the RCTs (9.9 percent) the absolute rate difference is estimated to be 6.7 percent (NNT = 15); however, when we use the rate of

cough with ACEIs equal to the cohort studies (1.7 percent) the absolute rate difference is estimated to be 1.1 percent (NNT = 87). The latter estimate is likely to be more clinically relevant.

Figure 5. Studies reporting on cough with ACEIs vs. ARBs



Withdrawals due to adverse events

Twenty-four (24) studies met our inclusion criteria and reported withdrawals due to adverse events.[12,14,21,23,27,32,34-39,41-45,47,48,52,57,61,63,65] Of these, two (eight percent) were of good methodological quality, 18 (75 percent) were fair in quality, and four (17 percent) were poor. Twenty-two 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 1213 patients, with a total of 7664 patients. Study durations ranged from 12 weeks to 5 years, with a mean of 49 weeks (median 25 weeks). The mean age of study participants was 55 years (SD 5). The proportion of female patients included ranged from 19 to 59 percent, with a mean of 46 percent. Fifteen studies (63 percent) reported the racial demographics of the study participants. Six of these (25 percent of the 24 total studies) enrolled a minimum of 10 percent of ethnic minority participants, while five enrolled only white patients.

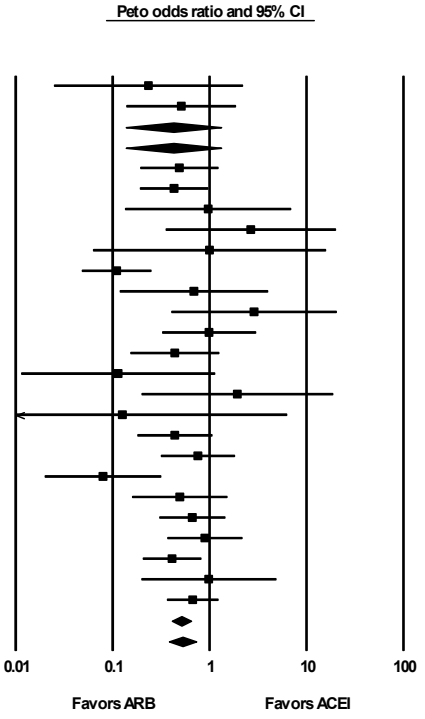
Rates of withdrawals due to adverse events ranged from 1 to 41 percent, with a mean of 10 percent (median 3 percent) for patients on ARBs, and a mean of 19 percent for patients on ACEIs (median 8 percent). Trials almost uniformly favored ARBs (i.e., there were more

withdrawals in ACEI-treated groups). However, there was significant variation in the study protocols and data reporting.

We conducted a meta-analysis of all 24 studies that reported withdrawals due to adverse events (Figure 6). Sixteen studies demonstrated higher rates in ACEI-treated participants; three studies demonstrated higher rates in ARB-treated participants; and five showed no difference in withdrawal rates. For the pooled odds ratio, the Q test and the I^2 between studies demonstrated modest heterogeneity between studies (Q = 36.0; I^2 = 36.2 percent). The meta-analysis revealed that the odds ratio (Peto) for withdrawal rate favored ARBs (0.51; 95 percent CI 0.38 to 0.70; random-effects model). For the median withdrawal rate (8 percent for ACEIs) the absolute difference in withdrawal rate is estimated to be 3.7 percent (NNT = 27).

Figure 6. Studies reporting withdrawals due to adverse events for ACEIs vs. ARBs

Model	Group by Studydesign	Outcome	Studyname	Peto odds ratio	Lower limit	Upper limit	p-Value
	OBS	Withdrawals	Avanza	0.23	0.02	2.23	0.21
	OBS	Withdrawals	Verdecchia	0.51	0.14	1.90	0.32
Fixed	OBS			0.42	0.14	1.30	0.13
Random	OBS			0.42	0.14	1.30	0.13
	RCT	Withdrawals	Cuspidi	0.49	0.19	1.25	0.13
	RCT	Withdrawals	McInnes	0.43	0.19	0.98	0.04
	RCT	Withdrawals	Mogensen	0.97	0.13	7.04	0.98
	RCT	Withdrawals	Scram	2.66	0.35	20.30	0.34
	RCT	Withdrawals	Elliot	1.00	0.06	16.03	1.00
	RCT	Withdrawals	Koylan	0.11	0.05	0.25	0.00
	RCT	Withdrawals	Coca	0.69	0.12	4.05	0.68
	RCT	Withdrawals	Mimran	2.88	0.40	20.73	0.29
	RCT	Withdrawals	Mallion	0.99	0.32	3.05	0.99
	RCT	Withdrawals	Roca-Cusachs	0.44	0.15	1.27	0.13
	RCT	Withdrawals	Derosa B	0.11	0.01	1.15	0.07
	RCT	Withdrawals	Lacourciere	1.94	0.20	19.03	0.57
	RCT	Withdrawals	Shand	0.13	0.00	6.37	0.30
	RCT	Withdrawals	Tikkanen	0.44	0.18	1.08	0.07
	RCT	Withdrawals	Townsend	0.76	0.31	1.85	0.54
	RCT	Withdrawals	Neutel	0.08	0.02	0.32	0.00
	RCT	Withdrawals	Amerena	0.49	0.16	1.55	0.23
	RCT	Withdrawals	Karlberg	0.66	0.30	1.47	0.31
	RCT	Withdrawals	Black	0.89	0.36	2.20	0.81
	RCT	Withdrawals	Malacco	0.41	0.20	0.83	0.01
	RCT	Withdrawals	Naidoo	0.98	0.20	4.93	0.98
	RCT	Withdrawals	Barnett	0.67	0.36	1.25	0.21
Fixed	RCT			0.51	0.40	0.64	0.00
Random	RCT			0.52	0.38	0.72	0.00



Caveats and concerns in relation to these data include the fact that only one study was 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.[70]

Adherence and Persistence

Nineteen papers describing 17 distinct studies reported at least some quantitative information on persistence or adherence.[16,17,19,25,38,41,42,50,57,67,71-79] 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 seven studies that measured pill counts. Studies of persistence – whether patients remain on the initial ACEI or ARB – included two RCTs as well as nine longitudinal cohorts in which patients were followed in a real-world setting. 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.,[57] adherence with ACEIs and ARBs was similar (Table 8). Moreover, adherence was high, above 97 percent in five of the seven studies assessed. All of the 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.[41] used a narrow range of 90 to 110 percent of prescribed pills, so might be expected to report lower adherence than Malmqvist et al.,[50] 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 8. Studies of adherence with ACEIs and ARBs

Study	Adherence with ACEIs	Adherence with ARBs	Definition of adherence
Amerena et al.[42]	99%	99%	Pill counts at 6 weeks
	98%	98%	Pill counts at 12 weeks
Coca et al.[38]	98.4%	98.3%	Taking 80-110% of pills
Koylan et al.[57]	~ 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.[50]	> 98%	> 98%	Taking 75-125% of pills at 6 weeks
	> 98%	> 98%	Taking 75-125% of pills at 12 weeks
McInnes et al.[41]	90%	90%	Taking 90-110% of pills
Rosei et al.[17]	98.2%	97.8%	Not specifically defined
Williams et al.[25]	> 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 9). 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.

Table 9. Studies of persistence with ACEIs and ARBs

Study	Duration	ACEIs			ARBs		
		Continued	Switched	Discontinued	Continued	Switched	Discontinued
Randomized trials							
Saito et al.[16]	6 mo	71%	28%	2%	89%	9%	2%
Koylan et al.[57]	6 mo	~ 82%	-	-	~ 89%	-	-
Longitudinal cohort studies							
Hasford et al.[19]	1 yr	42%	-	-	44.7 to 60.8%	-	-
Mazzaglia et al.[67]	1 yr	~ 50%	~ 8%	~ 42%	~ 50%	~ 10%	~ 40%
Bloom et al.[71]/Conlin et al.[73]	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.[76]	1 yr	59.7%	-	-	62.0%	-	-
Marentette et al.[77]	1 yr	-	-	~ 35%	-	-	~ 15%
Bourgault et al.[72]	1 yr	-	-	41%	-	-	34%
	2 yr	-	-	53%	-	-	44%
	3 yr	-	-	60%	-	-	47%
Burke et al.[79]	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.[78]	1 yr	50%	-	-	63%	-	-
Degli Esposti et al.[74,75]	1 yr	30.7%	9.4%	59.9%	33.4%	24.6%	42.0%

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.,[77] Bourgault et al.,[72] Burke et al.,[79] Wogen et al.,[78] and Degli Esposti et al.[74,75]) 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 characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?

Key Points

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

Blood Pressure

We did not identify any subgroup of patients in which one ACEI or ARB was clearly superior. Two of 50 studies reporting blood pressure outcomes included only women,[26,50] and two additional studies reported results for a female subgroup.[39,47] Three of these four found no significant difference in blood pressure effects between the ACEI and the ARB treatment arms; however, the largest of these studies 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; $p \leq 0.01$).[50] There were three studies conducted exclusively in elderly patients (age ≥ 65), and three additional studies that reported separate results for this age group.[13,28,33,35,39,47] Four of these studies showed no difference between ACEI and ARB treatment in elderly patients,[13,28,39,47] and two studies reported better blood pressure lowering in the ARB arm.[33,35] Eight studies were conducted only in diabetic patients with hypertension, none of which showed a difference between the two classes of medication.[11,12,17,21,23,40,52,60] In four studies, blood pressure was reported as an outcome in a subgroup of black patients.[15,30,35,44] 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.[35]

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 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 with regard to any specific subgroup. However, one study included only women in the study population.[50] 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.[70] 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.

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. However, some observations emerge regarding persistence with either agent (Table 10). 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 10. Predictors of persistence with ACEIs and ARBs

Study	Predictors of persistence
Mazzaglia et al.[67]	Increasing age, family history of cardiovascular diseases and diabetes, no severe hypertension, low chronic disease score
Bloom et al.[71] (1yr)/Conlin et al.[73] (4 yr)	1 yr: Increasing age, < 1 dose per day, male sex 4 yr: Increasing age, female sex
Erkens et al.[76]	Increasing age, male sex, antidiabetic drugs, lipid lowering drugs, previous cardiovascular hospitalizations
Marentette et al.[77]	Increasing age, female sex
Degli Esposti et al.[74] (1 yr)/Degli Esposti et al.[75] (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

Lipids

Several potentially relevant subgroups were identified, but none had a clear difference in outcomes for lipid parameters. Six studies evaluated patients with diabetes.[11,12,21,23,40,60] These included three that found small changes in various lipid parameters,[11,23,60] but the other three found none.[12,21,40] Other populations studied – including postmenopausal women,[26] Asians,[18] and Turks[60] – did not have detectable changes in the lipid profile.

Diabetes Markers

In the six studies requiring diabetes as an inclusion criteria, four found no difference in individuals receiving ACEIs or ARBs in glucose or HgbA1c levels;[12,21,40,60] one found no change in glucose but a small statistically significant increase in HgbA1c for the ARB (+0.25 percent enalapril, +0.6 percent losartan; data not reported for between-group comparisons);[23] and one found no change in HgbA1c but a decline in glucose levels for both which was statistically greater for the ACEI (perindopril -15 ± 4 mg/dL, candesartan -8 ± 2 mg/dL).[11] Thus, for the two studies for which a difference was found, the difference was discrepant (i.e., an increase in HgbA1c 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 HgbA1c were performed for several other subgroups including Asians,[18] Turks,[60] Brazilians,[65] and postmenopausal women.[26] None of these studies identified a difference in the impact of ACEIs and ARBs with regard to glucose or HgbA1c.

LV Mass/Function

Although five of the eight studies that presented results on LV mass or function demonstrated some decreases in LVMI, the sum of the evidence does not demonstrate a difference between ACEIs and ARBs with regard to their effect on LV mass or function for individuals with essential hypertension. No subgroup analyses were performed in the included studies 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 either ACEIs or ARBs 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 ACEIs versus ARBs 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 11). Second, we describe the nature and quality of the evidence in a format recommended by the GRADE Committee (Table 12). Finally, we summarize the quantitative analyses of outcomes, offering an estimate of the comparative outcomes for ACES (Table 13).

Table 11. Summary of evidence on comparative long-term benefits and harms of ACEIs vs. ARBs for essential hypertension

Key question	Strength of evidence	Conclusions
Key Question 1. For adult patients with essential hypertension, how do ACEIs and ARBs differ in the following health outcomes:		
a. Blood pressure control?	High	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 50 studies (47 RCTs, one nonrandomized controlled clinical trial, one retrospective cohort study, and one case-control study) in which 13,532 patients receiving an ACEI or an ARB were followed for periods from 12 weeks to 5 years (median 16.5 weeks). Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols.
b. Mortality and major cardiovascular events?	Moderate	Due to insufficient numbers of deaths or major cardiovascular events in the included studies, it was not possible to discern any differential effect of ACEIs versus ARBs for these critical outcomes. In nine studies that reported mortality, MI, or clinical stroke as outcomes among 3356 subjects, there were 16 deaths and 13 strokes reported. This may reflect low event rates among otherwise healthy patients and relatively few studies with extended followup.
c. Quality of life?	Low	No differences were found in measures of general quality of life; this is based on four studies, two of which did not provide quantitative data.
d. Rate of use of a single antihypertensive?	High	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.

Table 11. Summary of evidence on comparative long-term benefits and harms of ACEIs vs. ARBs for essential hypertension (continued)

Key question	Strength of evidence	Conclusions
e. Risk factor reduction and other intermediate outcomes?	Moderate (lipid levels, markers of carbohydrate metabolism/ diabetes control, progression of renal disease) to Low (progression to type 2 diabetes and LV mass/function)	There were no consistent differential effects of ACEIs versus ARBs on several potentially important clinical outcomes, including lipid levels, progression to type 2 diabetes mellitus, markers of carbohydrate metabolism/diabetes control, measures of LV mass or function, and progression of renal disease (either based on creatinine, GFR, or proteinuria). Relatively few studies assessed these outcomes over the long term.
Key Question 2. For adult patients with essential hypertension, how do ACEIs and ARBs differ in safety, adverse events, tolerability, persistence, and adherence?	High (cough, withdrawals due to adverse events) to Moderate (persistence/ adherence) to Low (angioedema)	ACEIs have been consistently shown to be associated with greater risk of cough than ARBs (pooled odds ratio [Peto] = 0.32). For RCTs, this translates to a difference in rates of cough of 6.7 percent (NNT = 15); however, for cohort studies with lower rates of cough, this translates to a difference of 1.1 percent (NNT = 87). This is generally consistent with evidence reviewed regarding withdrawals due to adverse events, in which the NNT is on the order of 27 – that is, one more withdrawal per 27 patients treated with an ACEI versus an ARB. There was no evidence of differences in rates of other commonly reported specific adverse events. Angioedema was reported only in patients treated with ACEIs; however, because angioedema was rarely explicitly reported in the included studies, it was not possible to estimate its frequency in this population. ACEIs and ARBs have similar rates of 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.
Key Question 3. Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?	Very low	Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs and ARBs for any particular patient subgroup.

Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); GFR = glomerular filtration rate; LV = left ventricular; MI = myocardial infarction; NNT = number-needed-to-treat; RCT(s) = randomized controlled trial(s)

Table 12. GRADE summary table

Studies	Design	Quality	Consistency	Directness	SD	SA	PB	DR	PC
Outcome: Blood pressure control									
50	RCTs (1 nonrandomized controlled trial, 1 cohort study, 1 case-control)	Confounded by additional treatments, dose escalation	Consistent results	Direct	-	-	-	-	-
Outcome: Mortality and major cardiovascular events									
9	RCTs	No serious limitations	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)									
7 – serious AEs 29 – overall AEs 24 – withdrawals due to AEs	RCTs (1 nonrandomized controlled trial; 1 case-control)	Variation in study protocols and data reporting	Consistent results	Direct	-	-	-	-	-
Outcome: Specific adverse events									
30	RCTs (3 cohort studies)	Variation in data reporting	Consistent results	Direct	-	-	-	-	-
Outcome: Persistence/adherence									
17	RCTs (9 cohort studies)	Variation in data reporting	Consistent results	Direct	-	-	-	-	-
Outcome: Rate of use of a single agent for blood pressure control									
22	RCTs (2 cohort studies, 1 case-control)	No serious flaws	Consistent results	Direct	-	-	-	-	-
Outcome: Lipid levels									
12	RCTs (1 case-control)	No serious flaws	Inconsistent results between studies and between lipid parameters	Direct	-	-	-	-	-
Outcome: Rates of progression to type 2 diabetes									
0	NA	NA	NA	NA	+	-	-	-	-

Table 12. GRADE summary table (continued)

Studies	Design	Quality	Consistency	Directness	SD	SA	PB	DR	PC
Outcome: Markers of carbohydrate metabolism/diabetes control									
13	RCTs (1 nonrandomized controlled trial, 1 case-control)	No serious flaws	Inconsistent results between head-to-head studies and placebo-controlled studies	Direct	-	-	-	-	-
Outcome: Measures of LV mass/function									
8	RCTs (1 nonrandomized controlled trial; 1 case-control)	Poor quality studies; small sample sizes	Consistent results	Direct	-	-	-	-	-
Outcome: Measures of kidney disease									
15 GFR	RCTs (1 nonrandomized controlled trial, 1 cohort study, 1 case-control)	Poor quality studies; different parameters measured	Consistent results	Direct	-	-	-	-	-
10 protei-nuria			Inconsistent results	Direct	-	-	-	-	-

Abbreviations: AE(s) = adverse event(s); DR = dose response; LV = left ventricular; PB = publication bias; PC = all plausible confounders would reduce the effect; RCT(s) = randomized controlled trial(s); SA = strong association (+ = very strong, ++ = extremely strong); SD = sparse data

Table 13. GRADE balance sheet

Outcome	Number of patients		Effect based on pooling		Quality	Relative importance
	ACEI	ARB	Effect (95% CI)	NNT		
BP reduction	~ 6700	~ 6700	-	-	High	Critical
Rate of use of a single antihypertensive for BP control	2668/7296 (37%)	2268/4714 (48%)	Risk difference 1.3% (-1.0 to 3.5%)	-	High	
Mortality and major CV events	1663	1659	-	-	Moderate	Critical
Morbidity/QoL	~ 550	~ 550	No difference detected	-	Low	-
Cough	1091/42,029 (2.6%)	203/19,949 (1%)	Peto odds ratio 0.32 (0.29 to 0.36)	15 to 87*	High	
Adverse events – withdrawals	216/3593 (6.0%)	126/4071 (3.1%)	Peto odds ratio 0.51 (0.38 to 0.70)	27	High	Critical

Table 13. GRADE balance sheet (continued)

Outcome	Number of patients		Effect based on pooling		Quality	Relative importance
	ACEI	ARB	Effect 95% CI	NNT		
Persistence/ adherence	~ 95% of ~ 1400 (pill count) ~ 30% to 60% of ~ 108,000 (continuation)	~ 95% of ~ 1500 (pill count) ~ 33% to 64% of ~ 40,100 (continuation)	-	-	Moderate	
Lipid levels	870	807	-	-	Moderate	-
Progression to type 2 diabetes	No data	No data	-	-	Low	-
Markers of carbohydrate metabolism/diabetes control	807	741	-	-	Moderate	-
Measures of LV mass/function	386	306	-	-	Low	-
Measures of kidney disease – creatinine/GFR	329	262	Effect size (SMD) 0.02 (-0.19 to 0.23)	-	Moderate	-
Measures of kidney disease – proteinuria	117	114	Effect size (SMD) -0.42 (-0.97 to 0.14)	-	Moderate	-

* The observed rates of cough appear much higher in RCTs than cohort studies; this is due to the higher detection when the patient is queried systematically for this symptom. Thus, based on the overall odds ratio of 0.32, when we use the rate of cough with ACEIs equal to the RCTs (9.9 percent) the absolute rate difference is estimated to be 6.7 percent (NNT = 15); however, when we use the rate of cough with ACEIs equal to the cohort studies (1.7 percent) the absolute rate difference is estimated to be 1.1 percent (NNT = 87). The latter estimate is likely to be more clinically relevant.

Abbreviations: BP = blood pressure; CI = confidence interval; CV = cardiovascular; GFR = glomerular filtration rate; LV = left ventricular; NNT = number-needed-to-treat; QoL = quality of life; SMD = standardized mean difference

Future Research

With the exception of rates of cough, the hypothesis that ACEIs and ARBs 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 research in this area should consider:

- Subgroups of special importance such as individuals 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.

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.

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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
DBP	Diastolic blood pressure
EF	Ejection fraction
EPC	Evidence-based Practice Centers
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HgbA1c	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

APPENDIXES

Appendix A: Exact Search Strings

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:
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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:

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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:
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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)
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)

* 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.

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 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. 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.

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

* 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.

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 unable to obtain copies of four articles (two 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 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).

Aberg H, Morlin C, Lithell H. Different long-term metabolic effects of enalapril and atenolol in patients with mild hypertension. EGTA Group. J Hum Hypertens 1995;9(2):149-53.

Agodoa LY, Appel L, Bakris GL, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA 2001;285(21):2719-28.

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[erratum appears in JAMA 2003 Jan 8;289(2):178]. JAMA 2002;288(23):2981-97.

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Anonymous. Hypertension in Diabetes Study. III. Prospective study of therapy of hypertension in type 2 diabetic patients: efficacy of ACE inhibition and beta-blockade. Diabet Med 1994;11(8):773-82.

Anonymous. Hypertension in Diabetes Study IV. Therapeutic requirements to maintain tight blood pressure control.[erratum appears in Diabetologia 1997 Mar;40(3):366]. Diabetologia 1996;39(12):1554-61.

Anonymous. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ 1998;317(7160):713-20.

Anonymous. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group[erratum appears in BMJ 1999 Jan 2;318(7175):29]. BMJ 1998;317(7160):703-13.

Arima H, Hart RG, Colman S, et al. Perindopril-based blood pressure-lowering reduces major vascular events in patients with atrial fibrillation and prior stroke or transient ischemic attack. Stroke 2005;36(10):2164-9.

Bakris GL, Weir MR, Shanifar S, et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. Arch Intern Med 2003;163(13):1555-65.

Berl T, Hunsicker LG, Lewis JB, et al. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy[summary for patients in Ann Intern Med. 2003 Apr 1;138(7):I43; PMID: 12667050]. Ann Intern Med 2003;138(7):542-9.

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Cocco G, Ettlin T, Baumeler HR. The effect of amlodipine and enalapril on blood pressure and neurohumoral activation in hypertensive patients with Ribbing's disease (multiple epiphysal dystrophy). Clin Cardiol 2000;23(2):109-14.

Contreras G, Greene T, Agodoa LY, et al. Blood pressure control, drug therapy, and kidney disease. Hypertension 2005;46(1):44-50.

Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359(9311):995-1003.

Davis BR, Piller LB, Cutler JA, et al. Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Circulation 2006;113(18):2201-10.

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Derosa G, Ragonesi PD, Mugellini A, et al. Effects of telmisartan compared with eprosartan on blood pressure control, glucose metabolism and lipid profile in hypertensive, type 2 diabetic patients: a randomized, double-blind, placebo-controlled 12-month study. Hypertens Res 2004;27(7):457-64.

Devereux RB, Dahlof B, Kjeldsen SE, et al. Effects of losartan or atenolol in hypertensive patients without clinically evident vascular disease: a substudy of the LIFE randomized trial. Ann Intern Med 2003;139(3):169-77.

Douglas JG, Agodoa L. ACE inhibition is effective and renoprotective in hypertensive nephrosclerosis: the African American Study of Kidney Disease and Hypertension (AASK) trial. Kidney Int Suppl 2003;(83):S74-6.

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Fossum E, Moan A, Kjeldsen SE, et al. The effect of losartan versus atenolol on cardiovascular morbidity and mortality in patients with hypertension taking aspirin: the Losartan Intervention for Endpoint Reduction in hypertension (LIFE) study. J Am Coll Cardiol 2005;46(5):770-5.

Gray A, Clarke P, Raikou M, et al. An economic evaluation of atenolol vs. captopril in patients with Type 2 diabetes (UKPDS 54). Diabet Med 2001;18(6):438-44.

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Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354(9192):1751-6.

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Himmelmann A, Hansson L, Hansson BG, et al. Long-term renal preservation in essential hypertension. Angiotensin converting enzyme inhibition is superior to beta-blockade. Am J Hypertens 1996;9(9):850-3.

Hoieggen A, Alderman MH, Kjeldsen SE, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 2004;65(3):1041-9.

Ibsen H, Wachtell K, Olsen MH, et al. Does albuminuria predict cardiovascular outcome on treatment with losartan versus atenolol in hypertension with left ventricular hypertrophy? A LIFE substudy. J Hypertens 2004;22(9):1805-11.

Iino Y, Hayashi M, Kawamura T, et al. Interim evidence of the renoprotective effect of the angiotensin II receptor antagonist losartan versus the calcium channel blocker amlodipine in patients with chronic kidney disease and hypertension: a report of the Japanese Losartan Therapy Intended for Global Renal Protection in Hypertensive Patients (JLIGHT) Study. Clin Exp Nephrol 2003;7(3):221-30.

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Julius S, Alderman MH, Beevers G, et al. Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy: the LIFE study. J Am Coll Cardiol 2004;43(6):1047-55.

Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363(9426):2022-31.

Kizer JR, Dahlof B, Kjeldsen SE, et al. Stroke reduction in hypertensive adults with cardiac hypertrophy randomized to losartan versus atenolol: the Losartan Intervention For Endpoint reduction in hypertension study. Hypertension 2005;45(1):46-52.

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Olsen MH, Fossum E, Hoieggen A, et al. Long-term treatment with losartan versus atenolol improves insulin sensitivity in hypertension: ICARUS, a LIFE substudy. J Hypertens 2005;23(4):891-8.

Papademetriou V, Farsang C, Elmfeldt D, et al. Stroke prevention with the angiotensin II type 1-receptor blocker candesartan in elderly patients with isolated systolic hypertension: the Study on Cognition and Prognosis in the Elderly (SCOPE). J Am Coll Cardiol 2004;44(6):1175-80.

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Reims HM, Oparil S, Kjeldsen SE, et al. Losartan benefits over atenolol in non-smoking hypertensive patients with left ventricular hypertrophy: the LIFE study. Blood Press 2004;13(6):376-84.

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van Dijk MA, Breuning MH, Duiser R, et al. No effect of enalapril on progression in autosomal dominant polycystic kidney disease. Nephrol Dial Transplant 2003;18(11):2314-20.

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Velussi M, Brocco E, Frigato F, et al. Effects of cilazapril and amlodipine on kidney function in hypertensive NIDDM patients. Diabetes 1996;45(2):216-22.

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Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288(19):2421-31.

Appendix C: Abstract and Full-Text Screening Criteria

Abstract Screening Instructions

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

- The study is a direct comparison (any study design) of an ACEI versus an ARB (see list below; additional antihypertensive therapy OK if the same in both groups);
- The study is an indirect comparison (RCT only) of either an ACEI or an ARB (see list below) versus another antihypertensive or placebo (additional antihypertensive therapy OK if the same in all groups);
- The study is an indirect comparison (RCT only) of a combination of an ACEI or an ARB (see list below) plus another antihypertensive versus another antihypertensive or placebo;
- 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;
- Dose comparison studies with no placebo arm;
- 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 **"R"** for **Review.**

For included studies, please mark:
- "AVA" if the study is a **direct comparison** of an ACEI versus an ARB;
- "AVO" if the study is an **indirect comparison** of either (1) an ACEI or an ARB versus some other antihypertensive or placebo OR (2) a combination of an ACEI or an ARB plus another antihypertensive versus an antihypertensive or placebo.

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

Thus, coding for each abstract should be either:

- **EX**
- **R**

- **IN AVA** (specify # weeks or # months follow-up, or write "NS" if length of follow-up not specified)
- **IN AVO** (specify # weeks or # months follow-up, or write "NS")

Included ACEIs
benazepril (Lotensin)
captopril (Capoten)
enalapril (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)

Direct ACEIs vs. ARBs Comparisons – Full-Text Screening Criteria

Note: Articles coded at the abstract screening stage as included, but having a treatment duration/followup lasting < 12 weeks (n = 88), were excluded at this stage without further review. The remaining 103 included abstracts with treatment duration/followup ≥ 12 weeks were reviewed in full-text form. 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:

ACEIS
benazepril (Lotensin)
captopril (Capoten)
enalapril (Vasotec; Enalaprilat IV)
fosinopril (Monopril)
lisinopril (Prinivil, Zestril)
moexipril (Univasc)
perindopril (Aceon)
quinapril (Accupril)
ramipril (Altace)
trandolapril (Mavik)

ARBS
candesartan cilexetil (Atacand)
eprosartan (Teveten)
irbesartan (Avapro),
losartan (Cozaar)
olmesartan medoxomil (Benicar)
telmisartan (Micardis)
valsartan (Diovan)

- ***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 or ARB not on above list

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:

- 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 [MI], 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:

- 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)
- Tolerability
- Persistence
- Adherence

6) Sample size:

- ***Exclude*** if total number of patients randomized to ACEI and ARB treatment arms < 20

7) Treatment duration/length of followup:

- ***Exclude*** if treatment duration or longest followup < 12 weeks

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] **Study design:** [Delete all but one] RCT, parallel-group RCT, crossover Other [specify] **Blinding:** [For each item, Yes/No/NR = not reported] - Patients: - Providers: - Assessors of outcomes: **Was allocation concealment adequate?** [e.g., computer-generated list or central randomization] Yes/No/NR **Baseline/run-in period:** [length & intervention, or NA = not applicable] **Washout period(s):** [crossover trials only; length]	**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 medications (n [%]):** **Comorbidities (n [%]):** **Recruitment setting:** [Inclusion/exclusion criteria: describe these as reported in article. If tolerability was assessed during run-in or used as an incl/excl criterion, please note this.]	[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 comorbidities.] **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 due to AEs, serious AEs reported, switch rates]	[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.]

Appendix D: Data Abstraction Form

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Duration of treatment: [post-baseline/run-in; days, weeks, months]	**Inclusion criteria:** **Exclusion criteria:**	**6) Specific adverse events:** [including, but not limited to: weight gain, impaired renal function, angioedema, cough]:	
	Duration of post-treatment followup: [days, weeks, months, or NA = not applicable]		**7) Persistence/adherence:** **8) Lipid levels:** **9) Progression to type 2 diabetes:** **10) Markers of carbohydrate metabolism/diabetes control:** [HbA1c, insulin or other diabetes med dosage, fasting plasma glucose, aggregated measures of serial glucose measurements] **11) LV mass/function:** **12) Creatinine/GFR:** **13) Proteinuria:**	

Appendix E: Evidence Table

Evidence Table. Direct comparator studies of ACEIs vs. ARBs

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Amerena, Pappas, Ouellet, et al., 2002 **#3620**	**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 **Duration of treatment:** 12 wk **Duration of post-treatment followup:** NA	**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 Baseline values: Telmisartan / Enalapril SBP: 159.9 ± 12.4 / 157.7 ± 13.2 DBP: 103.0 ± 6.3 / 101.6 ± 6.1	**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: Telmisartan: 20 (7.5%) Enalapril: 34 (13.2%) 6 serious AEs (treatment group NR), none 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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Concurrent medications (n [%]): No other antihypertensives **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** - Age > 18 - Mild to moderate essential HTN, 95 ≤ DBP ≤ 114 (or 104 in German and Czech sites) **Exclusion criteria:** - Mean SBP ≥ 180 - Secondary HTN - Uncorrected volume or sodium depletion - Severe renal impairment, renal artery stenosis, hepatic impairment, biliary obstructive disorders, electrolyte disturbances, primary aldosteronism, or hereditary fructose intolerance - Known sensitivity to any component of the placebo, telmisartan, or enalapril tablets - Pregnant women, breast-feeding, or women of childbearing potential not using a approved form of birth control	Discontinuation due to AEs: Telmisartan: 4 (1.5%) Enalapril: 8 (3.1%) **6) Specific adverse events:** Telmisartan (n = 265) / Enalapril (n = 257) HA 22 (8.3%) / 18 (7.0%) Cough 2 (0.8) / 23 (8.9) Musculoskel pain 12 (4.5) / 8 (3.1) Malaise/fatigue 6 (2.3) / 9 (3.5) Hypotension 3 (1.1) / 10 (3.9) Viral ENT infect 8 (3) / 7 (2.7) **7) Persistence/adherence:** Compliance assessed by pill count at clinic visit; similar in both 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	
Avanza, El Aouar, and Mill, 2000 **#5600**	**Geographical location:** Vitoria, Brazil **Study dates:** Unknown **Funding source:** Merck Sharp & Dhome – supplied meds **Interventions:** - Enalapril 20 mg qam + 15 mg qpm (n = 22)	**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)	**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	**General comments:** None **Quality assessment:** Overall rating: Poor Comments: - Poor study design - Non-randomized, non-blinded - Small sample size - Non-responders and non-compliant

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- 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) **Was allocation concealment adequate?:** No **Baseline/run-in period:** 12-day washout of prior meds **Duration of treatment:** 10 months **Duration of post-treatment followup:** NA	**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: SBP / DBP Enalapril 173 ± 2.9 / 104 ± 1.8 Losartan 170 ± 1.9 / 103 ± 1.7 Enalapril + losartan 173 ± 2.8 / 104 ± 1.5 24-hr ABPM also performed using a SpaceLabs 90207 device, with readings every 20 min **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** University clinics **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	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:** 4/22 patients (18%) in the enalapril group withdrew due to cough **6) Specific adverse events:** NR **7) Persistence/adherence:** 2/61 patients were noncompliant (both enalapril) 4/61 stopped taking study medication (2 losartan, 2 combination group) 2/61 altered medication schedule (both combination group) **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** 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. Baseline / 10 mo Enalapril (n = 15) 90 ± 4 / 90 ± 4 Losartan (n = 15) 93 ± 4 / 94 ± 4	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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			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) - Long-term use of corticosteroids, neuroleptics or antidepressants	**11) LV mass/function:** Mean LVMI (g/m^2) Baseline 10 mo Enalapril (n = 15) 141 ± 3.9 123 ± 3.6 Losartan (n = 15) 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. Baseline 10 mo 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 **#11010**	**Geographical location:** 39 centers in northern Europe (Denmark, Finland, The Netherlands, Norway, Sweden, and the UK) **Study dates:** NR **Funding source:** Boehringer Ingelheim	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 250 - Began treatment: 250 - Completed treatment: 168 - Withdrawals/losses to followup: 38 telmisartan group (20 due to AEs, 18 for other causes), 44 enalapril group	**1) Blood pressure:** Adjusted mean reduction in SBP over 5 yr (last observation carried forward): Telmisartan Enalapril 6.9 mm Hg 2.9 mm Hg 95% CI: -8.5 to 0.5 mm Hg Figure 2 demonstrates changes graphically.	**General comments:** - Primary outcome of study was change in GFR **Quality assessment:** Overall rating: Fair Comments: - Many dropouts; GFR data based on

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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	(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: Telmisartan / Enalapril 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%) **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%) **Recruitment setting:** Academic centers in northern Europe	% 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:** Telmisartan / Enalapril Stroke 6 / 6 CHF 9 / 7 Non-fatal MI 9 / 6 Incr Cr < 2.3 2 / 2 **5) Safety:** Telmisartan / Enalapril Any AE: 115 (95.8%) / 130 (100%) AE leading to study discontinuation: 20 (17%) / 30 (23%) **6) Specific adverse events:** See 4) above. Note that patients with know history of angioedema related to ACEIs were excluded. **7) Persistence/adherence:** NR **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.”	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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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 - 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	**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): GFR: Telmisartan (n = 103) -17.5; Enalapril (n = 113) -15.0; Change (95% CI) -2.6 (-7.1, 2.0) Creat: Telmisartan (n = 116) 0.10; Enalapril (n = 128) 0.10; Change (95% CI) 0 (-0.66, 0.65) **13) Proteinuria:** Mean change from baseline (last observation carried forward): UAE*: Telmisartan (n = 115) 1.03; Enalapril (n = 125) 0.99; Change (95% CI) 1.04 (0.71, 1.51) *UAE = urinary albumin excretion (ratio)	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Black, Graff, Shute, et al., 1997 **#6850**	**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 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**	**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 [%]):** 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	**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) 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%	**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 SBP values **Applicability:** - Setting not specified, study centers not reported - Unclear how patients recruited - Exclusion criteria vague on what "clinically significant" means

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	followup: NR	**Inclusion criteria:** - Age 21-80 yr - 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	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:** (see table below) **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	

	Valsartan (n = 364)	Lisinopril (n = 187)
Headache	7.7%	3.2%
Viral infection	0.3%	0%
URI	0.5%	0%
Fatigue	2.2%	3.7%
Back pain	0.3%	0%
Diarrhea	1.6%	2.1%
Cough	1.1%	8.0%
Dizzy	1.1%	3.7%
Sinusitis	0.3%	1.1%

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (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>Bloom, 1998

#12630

and

Conlin, Gerth, Fox, et al., 2001

#12640</td>
<td>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)
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</td>
<td>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)
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</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:
Based on prescription refill on or within 3 mo after 1-yr anniversary of initial prescription

1-year data:
<table>
<tr><th>Drug</th><th>Continued</th><th>Switched</th><th>D/c'd</th></tr>
<tr><td>ARB</td><td>64%</td><td>7%</td><td>29%</td></tr>
<tr><td>ACEI</td><td>58%</td><td>9%</td><td>33%</td></tr>
<tr><td>CCB</td><td>50%</td><td>9%</td><td>41%</td></tr>
<tr><td>Beta-B</td><td>43%</td><td>7%</td><td>50%</td></tr>
<tr><td>Thiaz</td><td>38%</td><td>6%</td><td>56%</td></tr>
</table>
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:
<table>
<tr><th>Drug</th><th>Continued</th><th>Switched</th><th>D/c'd</th></tr>
<tr><td>ARB</td><td>50.8%</td><td>16.5%</td><td>32.7%</td></tr>
<tr><td>ACEI</td><td>46.5%</td><td>18.9%</td><td>34.6%</td></tr>
<tr><td>CCB</td><td>40.7%</td><td>19.3%</td><td>40.0%</td></tr>
<tr><td>Beta-B</td><td>34.7%</td><td>12.7%</td><td>52.6%</td></tr>
<tr><td>Thiaz</td><td>16.4%</td><td>32.6%</td><td>51.0%</td></tr>
</table>
</td>
<td>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 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</td>
</tr>
</table>

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Exclusion criteria: - Prescription for nitrate, 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	- 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 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 **#12820**	**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 [%]):** 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:** Sample sizes at various timepoints: 1 year: ARBs 463, ACEIs 3456 2 years: ARBs 148, ACEIs 1541 3 years: ARBs 5, ACEIs 265 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	**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. Direct comparator studies of ACEIs vs. ARBs (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	**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	classes and add-on therapies. Cumulative persistence: ARBs ACEIs 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	
Burke, Sturken-boom, Lu, et al., 2006 **#12880**	**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	**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%	**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	**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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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 **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** NA **Duration of post-treatment followup:** 4 yr	**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 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	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% 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	- 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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			11) LV mass/function: NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Celik, Iyisoy, Kursak-lioglu, et al., 2005 **#890**	**Geographical location:** NR (author based in Turkey) **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	**Number of patients:** - Screened for inclusion: 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%) **Recruitment setting:** NR	**1) Blood pressure:** At 6 months, n = 50 each group: 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 **13) Proteinuria:** NR	**General comments:** None **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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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 **#4500**	**Geographical location:** Multicenter trial: 17 centers in Spain **Study dates:** NR **Funding source:** Sanofi-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	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: 295 - Randomized: 238 - Began treatment: 238 - Completed treatment: 226 - Withdrawals/losses to followup: 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%	**1) Blood pressure:** Posttreatment seated trough BP values not reported ABPM results: 24-hr BP at 12 wk: Irbesartan (n = 111) / Enalapril (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)	**General comments:** - Baseline 24-hour SBP significantly higher in irbesartan group (mean 4 mm p = 0.003) **Quality assessment:** Overall rating: Fair 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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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	**Race/ethnicity (n [%]):** 100% white **Baseline blood pressure:** *Clinic BP* using mercury sphygmomanometer: 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) 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	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: 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 due to AEs | 2 (1.7) | 3 (2.4) | AEs deemed probably related to treatment were	described - Process of inclusion of study centers not described - Comorbid conditions not described: they were "excluded" but list of criteria not mentioned

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (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>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</td><td>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

6) Specific adverse events:

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

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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (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	
Cuspidi, Muiesan, Valagussa, et al., 2002 **#3790**	**Geographical location:** 36 sites in Italy, France, Germany **Study dates:** NR **Funding source:** Takeda Italia **Interventions:** - Candesartan 8-16 mg qd (n = 115) - 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,	**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") - 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	**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 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	**General comments:** - Emphasis on a non-biased approach and interpretation of results **Quality assessment:** Overall rating: Fair Comments: - Would have been compelling if 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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	previous antihypertensive treatments withdrawn **Duration of treatment:** 48 weeks **Duration of post-treatment followup:** NA	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 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)	HCTZ): Candesartan: 61.0% Enalapril: 53.4% **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** There were no serious AEs Adverse events: **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):

	N (%)	Withdrawals (n)
Candesartan	16 (14%)	6
Enalapril	24 (19%)	13

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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			(n = 105)	
			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 **13) Proteinuria:** NR	
De Rosa, Cardace, Rossi, et al., 2002 **#4470**	**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	**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, but there was	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Duration of treatment: 3 years **Duration of post-treatment followup:** NA	Losartan / Enalapril SBP 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"	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): Losartan: Pre- 176 ± 24; Post- 124; Change (95% CI) -52 (-110.5, 32) Enalapril: Pre- 170 ± 19; Post- 129; Change (95% CI) -41(-90.3, 21.9) P-value for between-group difference NR **12) Creatinine/GFR:** GFR measured by renal scintigraphy at baseline and 3 yr (mL/min ± SD): | | Losartan | Enalapril | | Baseline | 96.5 ± 32.3 | 94.8 ± 31.1 | | 3 yr | 108.6 ± 31.1 | 99.8 ± 19.6 | | P-value | < 0.005 | 0.085 | **13) Proteinuria:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Degli Esposti, Degli Esposti, Valpiani, et al., 2002 **#12800** **(1-year results)** ***and*** **Degli Esposti, Sturani, Di Martino, et al., 2002** **#12810** **(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 **Duration of treatment:** NR **Duration of post-treatment followup:** Data reported for 1 and 3 years	**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% 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	**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. 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	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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	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	
Derosa, Cicero, Ciccarelli, et al., 2003 **#3140**	**Geographical location:** Pavia, Italy **Study dates:** NR **Funding source:** NR **Interventions:** - Perindopril 4 mg (n = 49) - Candesartan 16 mg (n = 47) Dose titration and co-interventions: No titration; no co-interventions allowed **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: NR - Assessors of outcomes: Yes **Was allocation concealment adequate?:** Yes **Baseline/run-in period:** 4-wk placebo run-in **Duration of treatment:** 12 mo	**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:** 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	**1) Blood pressure:** Mean change (± SD) in BP from baseline to 12 mo: Perindopril / Candesartan 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 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.	**General comments:** - Probably underpowered study **Quality assessment:** Overall rating: Good **Applicability:** - Very early diabetes with mild hypertension - Patients in academic medical center in Italy - Probably underpowered to detect true differences between the groups

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Duration of post-treatment followup: Patients followed for an additional month at the end of the trial after discontinuation of study meds	**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 **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	**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 HDL change 12 mo: -2 ± 0.5 / +2 ± 0.4 TG baseline: 160 ± 18 / 149 ± 10 TG change 12 mo: -22 ± 11.6 / +2 ± 0.8 * 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: Perindopril / Candesartan HbA1c baseline: 6.4 ± 0.9 / 6.5 ± 1.1 HbA1c change 12 mo: -0.2 ± 0.1 / -0.2 ± 0.1 Fasting glucose baseline: 155 ± 15 / 160 ± 13	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Fasting glucose 1 yr: -15 ± 4* (Perindopril); -8 ± 2 (Candesartan) * 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 **13) Proteinuria:** Values are mean ± SD: AER/24 hr baseline: 17 (10) (Perindopril); 18 (11) (Candesartan) AER/24 hr change 12 mo: -8 ± 3.6 (Perindopril); -8 ± 4.1 (Candesartan) 6-mo and 1-mo posttreatment followup data also reported	
Eguchi, Kario, and Shimada, 2003 **#3150**	**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 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	**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 Range: NR **Sex (n [%]):** Female: 57% Male: 43%	**1) Blood pressure:** Mean seated trough BP at 12 wk: SBP: 148 ± 16 (Candesartan, n = 61); 144 ± 18 (Lisinopril, n = 61) DBP: 79 ± 11 (Candesartan); 77 ± 9.8 (Lisinopril) No significant difference between groups (p-values NR) Other outcomes reported: 24-hr ABPM outcomes **2) Rate of use of a single antihypertensive agent for BP control:** Trichlormethazide added per protocol: Candesartan: 79% Lisinopril: 80% p = NS	**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 after period 1 of crossover, imbalance in treatment groups (apparently due to more patients discontinuing lisinopril and not continuing to period 2)

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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	**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 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	**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	- 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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Elliott, 1999 **#5950** *and* **Gavras and Gavras, 1999** **#6030** *and* **Levine, 1999** **#6020** *and* **Argenziano and Trimarco, 1999** **#6040** *and* **Breeze, Rake, Donoghue, et al., 2001** **#4660**	**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 **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	**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 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%)	**1) Blood pressure:** Mean post-treatment BP values NR Overall study population Mean change in BP from baseline (at 26 wk): Enalapril / Eprosartan 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): Enalapril / Eprosartan 12 wk 62.6% / 70.3% (p < 0.05) 26 wk 73.4% / 81.7% (p < 0.02) ≥ 65 years subgroup Mean change in BP from baseline (at 26 wk): Enalapril / Eprosartan Sit SBP -15.3 ± 2.2 / -18.9 ± 2.1 (NS) Sit DBP -12.2 ± 1.1 / -13.9 ± 1.1 (NS) Response rates: Enalapril / Eprosartan 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	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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 tachyarrhythmias, bradycardia - Unstable DM - Clinically significant renal or hepatic disease - Other concurrent severe disease - Emphysema, chronic bronchitis, asthma with cough, URI < 2 wks	**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. 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%) 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	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			8) Lipid levels: Eprosartan: baseline / end; Enalapril: 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	
Erkens, Panneman, Klungel, et al., 2005 **#12840**	**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	**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%)	**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%	**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. Direct comparator studies of ACEIs vs. ARBs (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:** NR **Duration of post-treatment followup:** Patients followed for 15 mo after their index data	**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% **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	Persistence increased with male sex, increasing 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 **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Fogari, Mugellini, Zoppi, et al., 2002 **#4320**	**Geographical location:** Pavia, Italy **Study dates:** NR **Funding source:** NR **Interventions:** - Perindopril 4 mg daily (n = 42) - 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	**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) **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	**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 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 197 ± 23 / 186 ± 19 / NS Losartan 191 ± 20 / 188 ± 19 / NS Mean triglycerides (mg/dL): Baseline / 12 wk / p-value Perindopril 142 ± 49 / 127 ± 44 / NS	**General comments:** None **Quality assessment:** Overall rating: Fair 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 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. Direct comparator studies of ACEIs vs. ARBs (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	Losartan 145 ± 50 140 ± 48 NS **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** Mean FBG (mg/dL): Baseline / 12 wk / p-value Perindopril 112 ± 7.3 / 107 ± 6.9 / NS Losartan 113 ± 7.5 / 111 ± 7.0 / NS Mean HbA1c (%): Baseline / 12 wk / p-value Perindopril 7.2 ± 1.9 / 7.1 ± 1.7 / NS Losartan 6.9 ± 2.0 / 7.0 ± 1.8 / NS **11) LV mass/function:** NR **12) Creatinine/GFR:** Mean serum creatinine (mg/dL): Baseline / 12 wk / p-value Perindopril 1.1 ± 0.4 / 1.1 ± 0.4 / NS Losartan 1.1 ± 0.5 / 1.1 ± 0.4 / NS **13) Proteinuria:** NR	
Fogari, Mugellini, Zoppi, et al., 2004 **#2490**	**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	**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%)	**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	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- 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	**Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Trough seated BP measured using a standard mercury sphygmomanometer 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 [%]):** 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	**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 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	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Fogari, Zoppi, Preti, et al., 2001 **#4790**	**Geographical location:** Pavia, Italy **Study dates:** NR **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	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 89 - Began treatment: 89 - 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 (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)	**1) Blood pressure:** Mean trough seated BP at 12 wk: Trandolapril / Losartan SBP 145.2 ± 10 / 145.5 ± 11 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 231 ± 31 / 226 ± 29 / NS Losartan 227 ± 33 / 224 ± 31 / NS Mean triglycerides (mg/dL): Baseline / 12 wk / p-value Trandolapril 128 ± 59 / 125 ± 57 / NS Losartan 120 ± 51 / 123 ± 50 / NS **9) Progression to type 2 diabetes:** NR	**General comments:** None **Quality assessment:** Overall rating: Fair 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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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	**10) Markers of carbohydrate metabolism/diabetes control:** Mean FBG (mg/dL): Trandolapril: Baseline 92 ± 10; 12 wk 89 ± 10; p-value NS Losartan: Baseline 93 ± 9; 12 wk 92 ± 10; p-value NS Mean glucose infusion rate (GIR) (mg/min/kg): Trandolapril: Baseline 6.67 ± 0.56; 12 wk 7.99 ± 0.65; p-value < 0.05 Losartan: Baseline 6.74 ± 0.47; 12 wk 6.96 ± 0.50; p-value NS p = significant (but not specified) for between-group comparison **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Franke, 1997 **#11930**	**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 - Providers: Yes - Assessors of outcomes: 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 using a fully automated device (Bosotron 2) Baseline values NR	**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 **2) Rate of use of a single antihypertensive agent for BP control:** No other antihypertensives permitted	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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	**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	**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 **#3330**	**Geographical location:** NR **Study dates:** June 1999-Dec 2001 **Funding source:** NR **Interventions:** Multi-therapy trial (nifedipine, amlodipine, atenolol, nebivolol, telmisartan, and perindopril); total study was 40 normotensive controls and 180 treated patients	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 180 - 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	**1) Blood pressure:** At 6 months: Telmisartan / Perindopril SBP 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)	**General comments:** - Patients in multiple arms with small control group **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.)

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- 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	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 **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	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 LDL: Telmisartan / Perindopril 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: Telmisartan / Perindopril Baseline 97 ± 8 / 96 ± 7 6 mo 97 ± 8 / 97 ± 5 **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	- No data on race/ethnicity of subjects - No data on safety/adverse events **Applicability:** - Limited by few comorbidities and multiple comparisons

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Gregoire, Moisan, Guibert, et al., 2001 **#5090**	**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 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)	**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 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	**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%) 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 [%]): Losartan / ACEI / CCB 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 **8) Lipid levels:** NR	**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 **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. Direct comparator studies of ACEIs vs. ARBs (continued)

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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Hasford, Mimran, and Simons, 2002 **#4090**	**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 **Blinding:** - Patients: NA - Providers: NA - Assessors of outcomes: NA **Was allocation concealment adequate?:** NA	**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 Diuretics: 160.7 ± 20.4 / 93.8 ± 12.6 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR	**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, 24.5% losartan, 25.3% all other agents) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** 12.9% overall (9% irbesartan, 8% losartan,	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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" **Inclusion criteria:** - Newly diagnosed hypertension (< 1 yr) - Initial therapy with single agent **Exclusion criteria:** - Hypertension > 1 yr - Initial prescription for dual agents	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 **6) Specific adverse events:** NR **7) Persistence/adherence:** Persistence status determined on basis of filled prescriptions See outcome 2, above, for overall persistence rates 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 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	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Karlberg, Lins, and Hermans-son, 1999 **#6090**	**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 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	**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 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)	**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 / Enalapril 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 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.	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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 - 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	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:** 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 **12) Creatinine/GFR:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			13) Proteinuria: NR	
Kavgaci, Sahin, Onder Ersoz, et al., 2002 **#4040**	**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 **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	**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 ± 1.25 / NS Fosinopril 5.97 ± 1.3 / 5.34 ± 0.72 / < 0.05 Mean triglycerides (mmol/L): Baseline / 6 mo / p-value 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	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			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 **13) Proteinuria:** Mean albumin excretion (mg/day) in subgroup with microalbuminuria: Baseline 6 mo p-value Losartan (n = 8) 121 (32.0-264.5) 54.8 (8.6-261.0) < 0.05 Fosinopril (n = 7) 154 (44-300) 14 (10.6-46.0) < 0.05	
Koylan, Acarturk, Canberk, et al., 2005 **#860**	**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)	**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	**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	**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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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 patients/physician) **Baseline/run-in period:** None **Duration of treatment:** 6 months **Duration of post-treatment followup:** 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 Supine SBP: 160.9 ± 16.2 / 159.6 ± 15.2 / 160.7 ± 14.0 Supine DBP: 96.2 ± 7.4 / 96.5 ± 7.5 / 95.9 ± 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:**	**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%) 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 **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	differences in Table 1

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Secondary HTN - DBP ≥ 110 mmHg - 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		
Lacourciere, Belanger, Godin, et al., 2000 **#5550**	**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 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.	**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%) 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	**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 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	**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 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. Direct comparator studies of ACEIs vs. ARBs (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: 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	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) - 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	**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 **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).	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Lacourciere, Neutel, Davidai, et al., 2006 **#100**	**Geographical location:** 81 U.S. and Canadian sites **Study dates:** Oct 1, 2002 to July 17, 2003 **Funding source:** NR **Interventions:** Forced titration of: - Ramipril 2.5, 5, and 10 mg (n = 407) - Telmisartan 40 and 80 mg (n = 405) **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, placebo run-in phase 2-4 wk **Duration of treatment:** 14 wk **Duration of post-treatment followup:** NR	**Number of patients:** - 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 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: Telmisartan / Ramipril 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 ≤ 109	**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 / < 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 to be drug-related:	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: - Patients and providers not blinded **Applicability:** - Significant number of limitations to inclusion in the study as evidence by number of screened patients to enrolled

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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	<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:** Monitored via an unspecified process but 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	
Larochelle, Flack, Marbury, et al., 1997 **#6790**	**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	**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%)	**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	**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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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 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	**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 Irbesartan / Enalapril 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 (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	**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 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 9.9% / 13.1% *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	**Applicability:** - Patient compliance not assessed

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (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>12) Creatinine/GFR: NR

13) Proteinuria: NR</td><td></td></tr>
<tr><td>Mackay, Pearce, and Mann, 1999

#12650</td><td>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 mo

Duration of post-treatment followup: Up to 6 mo</td><td>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 general practitioners were mailed a questionnaire

Exclusion criteria:</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:
Patients with cough:
<table><tr><th>Drug</th><th>Pts w/ cough</th><th>Rate per 1000 pt-mo</th><th>95% CI</th></tr><tr><td>Enalapril</td><td>86</td><td>3.9</td><td>3.1 to 4.8</td></tr><tr><td>Lisinopril</td><td>270</td><td>14</td><td>13 to 16</td></tr><tr><td>Perindopril</td><td>210</td><td>16</td><td>14 to 19</td></tr><tr><td>Losartan</td><td>64</td><td>3.1</td><td>2.4 to 4.0</td></tr></table>Rate ratios for cough, day 8 to 60, compared to losartan:<table><tr><th>Drug</th><th>RR crude</th><th>RR adj for age and sex</th><th>95% CI</th></tr><tr><td>Enalapril</td><td>1.3</td><td>1.5</td><td>1.2 to 2.2</td></tr><tr><td>Lisinopril</td><td>4.6</td><td>4.8</td><td>3.6 to 6.5</td></tr><tr><td>Perindopril</td><td>5.3</td><td>5.7</td><td>4.2 to 7.6</td></tr></table>Rate ratios for cough; females compared with males<table><tr><th>Drug</th><th>RR crude</th><th>RR adj for age</th><th>95% CI</th></tr><tr><td>Enalapril</td><td>1.5</td><td>1.4</td><td>0.8 to 2.5</td></tr><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></td><td>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</td></tr>
</table>

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		NR, but presumably failure of GP to return questionnaire	**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, Santonastaso, Vari, et al., 2004 **#2130**	**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 - Assessors of outcomes: Yes **Was allocation concealment adequate?:** Yes **Baseline/run-in period:** 2-wk	**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 mercury sphygmomanometer; mean of 3 readings used Mean baseline values (± SD):	**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% Lisinopril: 78.7% **3) Mortality:** No deaths occurred during trial **4) Morbidity:** NR	**General comments:** None **Quality assessment:** Overall rating: Good **Applicability:** - Setting/recruitment/selection NR - Exclusion criteria strict and vague

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	placebo run-in **Duration of treatment:** 16 wk **Duration of post-treatment followup:** NA	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, ACEI, or thiazides - Pregnant, possibly pregnant, or breastfeeding women - Women of childbearing age not using birth control	**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) 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 **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Mallion, Bradstreet, Makris, et al., 1995 **#12090**	**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 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	**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%) 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	**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): Losartan: 55/109 (50.5%) Captopril: 15/51 (29%) p ≤ 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:**	**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 **Applicability:** - Minimal racial diversity (89% Caucasian) - Recruitment setting(s) not described - Minimal comorbidities in study population of hypertensive patients

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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 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	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%) **6) Specific adverse events:** AEs occurring in > 4% of patients in either group: Losartan (n = 109) n (%) DR / Captopril (n = 54) n (%) 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 **#5650**	**Geographical location:** 56 centers, locations not reported **Study dates:** NR **Funding source:** Astra Hässle AB **Interventions:** - Candesartan 8 to 16 mg (n = 140) - Enalapril 10 to 20 mg (n = 146) - HCTZ 12.5 to 25 mg (n = 143)	**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) **Age:** Mean: 57.7	**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 DBP -11 / -9 Mean difference between treatments (candesartan vs. enalapril) in change in seated	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: - Mean baseline and post-treatment BP values NR - Patients withdrawn from study if mean seated SBP > 200 mm Hg or DBP >

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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	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 **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	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 due to AEs; treatment groups not specified **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	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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Severe concomitant disease that may interfere with assessment - Any condition associated with poor compliance (e.g., drug or alcohol abuse)	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 **#12830**	**Geographical location:** Saskatchewan, Canada (database including > 90% of provincial residents) **Study dates:** Jan 1994-Dec 1998 **Funding source:** Merck Frosst Canada, Ltd. **Interventions:** Number of patients with data for at least 180 days: ARBs (n = 267) ACEIs (n = 7466) Beta-blockers (n = 4295) CCBs (n = 3200) Diuretics (n = 9623) Alpha-blockers (n = 731) Alpha-agonists (n = 575) Vasodilators (n = 25) Mixed classes (more than 1 class concurrently or sequentially during study period; n = 20,276) **Study design:** Retrospective cohort study **Blinding:**	**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: NA **Age (ARBs and ACEIs):** Mean: 58 Median: NR Range: 1-85 **Sex (ARBs and ACEIs; %):** Female: 48.8% Male: 51.2% **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** Population-based prescription drug database	**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 180 days: 267 / 7466 360 days: 170 / 6539 540 days: 44 / 5699 720 days: 3 / 4826 Small ARB sample explained by fact that ARBs not listed in provincial formulary until March 1996. 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.	**General comments:** - Relatively small number of patients in ARB subgroup **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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- 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 minimum of 180 days to a maximum of 720 days	**Inclusion criteria:** - ICD-9 code diagnosis of hypertension (401, 402, 403, 404, or 4-digit codes included in these categories) - At least 1 antihypertensive prescription during first 4.5 yr of study period - No antihypertensive prescription in the 12 mo before the first prescription **Exclusion criteria:** None specified	Extrapolating from Figure 2, persistence was: ARBs ACEIs 180 days 87% 75% 360 days 85% 65% 540 days - 60% 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 **#12110**	**Geographical location:** Honjo, Ashikaga, Tochigi, Japan **Study dates:** 1998-1999 **Funding source:** NR **Interventions:** - ACE group - perindopril 2 mg or	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 52 - Began treatment: 52 - Completed treatment: 52 - Withdrawals/losses to followup: 0 **Age:**	**1) Blood pressure:** Mild proteinuria Mod proteinuria SBP ACE ARB ACE ARB Baseline 148±3 154±4 152±4 150±3 12 wk 135±3 137±3 134±4 137±4 24 wk 132±4 NR 120±3 NR 48 wk 131±4 NR 124±3 NR	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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	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: ACE n = 13, ARB n = 13; Mod proteinuria: 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) - 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	Mild proteinuria: ACE / ARB; Mod proteinuria: ACE / ARB DBP 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 **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)	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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Mazzaglia, Mantovani, Sturken-boom, et al., 2005 **#390**	**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 **Blinding:** NA **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** 365 days **Duration of post-treatment followup:** NA	**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%) **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)	**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 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.	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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:** - 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	(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 **13) Proteinuria:** NR	
McInnes, O'Kane, Istad, et al., 2000 **#5680**	**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	**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%)	**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):	**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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Study design: RCT, parallel-group **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	**Race/ethnicity (n [%]):** Caucasian: 348 (99%) **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 - 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	Candesartan/HCTZ: 129/237 (54.4%) Lisinopril/HCTZ: 72/116 (62.1%) 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% Headache 11.8% / 8.5% Viral infection 8.8% / 7.7% Fatigue 5.9% / 6.0 Back pain 5.5% / 5.1% Resp infection 5.5% / 9.4% Pain 5.0% / NR Cough 4.6% / 23.1% Myalgia 4.2% / 6.0% Nausea 4.2% / NR Accident/injury NR / 4.3% Pharyngitis NR / 4.3% **7) Persistence/adherence:** As assessed by	change observed is unclear; would have been better to have placebo run-in to get baseline BP or at least to group results by 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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			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	
Mimran, Ruilope, Kerwin, et al., 1998 **#6640**	**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	**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.	**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:	**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. Direct comparator studies of ACEIs vs. ARBs (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>- Assessors of outcomes: NR

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</td><td>Baseline seated BP:

<table>
<tr><th></th><th>Enalapril</th><th>Irbesartan</th></tr>
<tr><td>SBP:</td><td>164.9 ± 12.8</td><td>163.9 ± 12.5</td></tr>
<tr><td>DBP:</td><td>101.8 ± 4.2</td><td>101.0 ± 4.1</td></tr>
</table>
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</td><td>- Mean DBP was higher in those titrated than those maintained at lowest dosages.
- 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:

<table>
<tr><th></th><th>Enalapril (%) (n = 102)</th><th>Irbesartan (%) (n = 98)</th></tr>
<tr><td>Adverse drug experience</td><td>26</td><td>19</td></tr>
<tr><td>AE</td><td>43</td><td>45</td></tr>
<tr><td>Serious AE</td><td>1.0</td><td>4.1</td></tr>
<tr><td>Discontinued</td><td>2.9</td><td>1.0</td></tr>
</table>
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

11) LV mass/function: NR

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

<table>
<tr><th></th><th>Enalapril n = 96</th><th>Irbesartan n = 94</th></tr>
</table></td><td></td></tr>
</table>

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Creatinine (mg/dL) | 0.03 (0 to 0.06) | 0.01 (-0.02 to 0.04) **13) Proteinuria:** NR	
Mogensen, Neldam, Tikkanen, et al., 2000 **#5340**	**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 **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	**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 **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%"	**1) Blood pressure:** Mean post-treatment BP values NR (except in Figure 2) Mean reduction (95% CI) in seated trough BP at 12 wk: | | Cande-sartan (n = 99) | Lisinopril (n = 98) | Adjusted* mean diff. between groups | |---|---|---|---| | SBP | 12.4 (9.1 to 15.8) | 15.7 (12.2 to 19.2)* | 3.3 (-1.5 to 8.2) p = 0.18 | | DBP | 9.5 (7.7 to 11.2) | 9.7 (7.9 to 11.5) | 0.02 (-2.3 to 2.7) p > 0.20 | *Adjusted for center, treatment, baseline value, weight, and change in DBP Mean reduction (95% CI) in seated trough BP at 24 wk: | | Candesartan (n = 49) | Lisinopril (n = 46) | |---|---|---| | SBP | 14.1 (8.9 to 19.2) | 16.7 (11.4 to 21.9) | | DBP | 10.4 (7.7 to 13.1) | 10.7 (8.0 to 13.5) | No statistical tests reported for comparison between candesartan and lisinopril monotherapies at 24 wk **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	**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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	placebo run-in **Duration of treatment:** 24 wk **Duration of post-treatment followup:** NA	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 - 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	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:** 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: Candesartan (n = 99): 30 (15 to 42) Lisinopril (n = 98): 46 (35 to 56) Adjusted* mean diff. between treatments: 30 (1 to 71) p = 0.58	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Adjusted for center, treatment, baseline value, weight, and change in DBP Mean reduction in urinary albumin:creatinine ratio (%, with 95% CI) at 24 wk: Candesartan (n = 49): 24 (0 to 43) Lisinopril (n = 46): 39 (20 to 54) Adjusted mean diff. between treatments: Not reported *Adjusted for center, treatment, baseline value, weight, and change in DBP	
Naidoo, Sareli, Marin, et al., 1999 **#6140**	**Geographical location:** 21 centers in South Africa, Hungary, 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	**Number of patients:** - Screened for inclusion: 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	**1) Blood pressure:** Mean BP at 12 wk (entire sample): SBP: Losartan/HCTZ (n = 173) 139.7 ± 17.6; Enalapril/HCTZ (n = 173) 140.5 ± 15 DBP: Losartan/HCTZ 88.7 ± 10.1; Enalapril/HCTZ 88.4 ± 8.3 Mean BP for patients *not* receiving adjunctive amlodipine: SBP baseline: Losartan/HCTZ (n = 129) 159.8 ± 13.7; Enalapril/HCTZ (n = 124) 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):	**General comments:** - 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 **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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Blinding: - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 2 days no meds **Duration of treatment:** 12 wk **Duration of post-treatment followup:** NA	mercury sphygmomanometer; average of 3 readings used Losartan/HCTZ / Enalapril/HCTZ SBP 162.9 ± 16.1 / 163.8 ± 16.1 DBP 104.2 ± 6.3 / 103.6 ± 7.4 **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	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 **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	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Need for treatment with beta-blockers, psychotropics, antidepressants, cimetidine, oral contraceptives, steroids, corticotropin, or lithium	**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	
Neutel, Frishman, Oparil, et al., 1999 **#5930**	**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 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	**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 [%]):** White: 433 (75%) Black: 102 (18%) Hispanic: 35 (6% Other: 8 (1%) **Baseline blood pressure:**	**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% **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Drug-related AEs: Telmisartan: 28% Lisinopril: 40% p = 0.001	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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	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	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 **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Rabbia, Silke, Carra, et al., 2004 **#12280**	**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) **Concurrent medications (n [%]):** None allowed during study **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** - Never treated mild hypertension	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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 **#3630**	**Geographical location:** 105 outpatient French Centers **Study dates:** NR **Funding source:** NR **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**	**Number of patients:** - Screened for inclusion: 671 - Eligible for inclusion: 441 - Randomized: 441 - Began treatment: 441 - Completed treatment: NR - Withdrawals/losses to followup: 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%)	**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 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	**General comments:** - Focus of article was comparison of self-measurement of BP and office measurement **Quality assessment:** Overall rating: Poor 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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	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	**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 [%]):** 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	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 **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	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Rajzer, Klocek, and Kawecka-Jaszcz, 2003 **#3320**	**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 = 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	**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):** 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	**1) Blood pressure:** Mean BP at 3 mo: | | Quinapril (n = 38) | Losartan (n = 24) | |---|---|---| | SBP | 141 ± 23.7 | 132 ± 15.8 | | DBP | 92 ± 8.7 | 83 ± 9.2 | Mean BP at 6 mo: | | Quinapril (n = 38) | Losartan (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)	**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 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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		drug monotherapy **Exclusion criteria:** NR	**12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Robles, Angulo, Grois, et al., 2004 **#12300**	**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 **Duration of post-treatment followup:** NA	**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:** - 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	**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 **13) Proteinuria:** 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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Heart failure - Hypokalemia - COPD - Hematological disease - Hb ≤ 13 gm or >17 gm - Hypersensitivity to test drugs - Pre-menopausal women		
Roca-Cusachs, Oigman, Lepe, et al., 1997 **#6710**	**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:** 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	**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%) **Baseline blood pressure:** Trough seated BP assessed using mercury sphygmomanometer after 5-min rest; average of 3 readings SBP: Losartan 158.2 ± 16.5; Captopril 157.2 ± 16.7 DBP: Losartan 103.9 ± 6.5; Captopril 103.2 ± 7.1 **Concurrent medications (n [%]):** Other BP meds not permitted **Comorbidities (n [%]):** NR	**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: SBP: Losartan (n = 190) -15.4; Captopril (n = 203) -12.2; P-value = 0.023 DBP: Losartan -11.5; Captopril -9.3; P-value = 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) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** ≥ 1 clinical AE: Losartan (n = 192) 63 (33%); Captopril (n = 204) 83 (41%) ≥ 1 drug-related clinical AE: Losartan 20 (10%); Captopril 27 (13%) ≥ 1 serious clinical AE: Losartan 4 (2%); Captopril 10 (5%) Withdrawn due to clinical AEs: Losartan 5 (3%); Captopril 12 (6%)	**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 to the general population

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Duration of treatment: 12 wk **Duration of post-treatment followup:** NA	**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 - 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	≥ 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). 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	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Rosei, Rizzoni, Muiesan, et al., 2005 **#1480**	**Geographical location:** Italy **Study dates:** NR **Funding source:** Takeda Italia Farmeceutici S.p.A., Rome, Italy **Interventions:** - Candesartan 8-16 mg (n = 66) - 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	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 129 - Began treatment: 129 - Completed treatment: 118 - Withdrawals/losses to followup: 11 **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% **Recruitment setting:** NR	**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 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) Baseline: 145.5 ± 79.5 / 143.9 ± 111.5	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: - Assembly of patients not described **Applicability:** - Patient identification, study site not clear - All patients had NIDDM

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			24 wk 159.1 ± 95.3 154.8 ± 160.5	
		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	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	
		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 - Serum creatinine > 1.6 mg/dL - Severely impaired liver function, serum sodium ≤ 130 mmol/L, serum K ≤ 3.6 mmol/L	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Ruff, Gazdick, Berman, et al., 1996

#7110

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 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

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 sphygmomanometer after 5 min rest; average of 3 readings taken at 1-min intervals

	Losartan	Enalapril
SBP	173.7 ± 14.5	176.5 ± 14.9
DBP	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)

1) Blood pressure:
Seated trough BP:

	Los-pre	Los-12 wk	Enal - pre	Enal - 12 wk
SBP	173.7 (14.5)	140.3 (16.1)	176.5 (14.9)	133.8 (14.5)
DBP	118 (3.6)	90.8 (8.7)	119 (3.1)	88.4 (5.1)

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:

	Non-black		Black	
	Losart	Enal	Losart	Enal
Pre-	172.5 (15.4)	180.3 (15.3)	175.2 (13.6)	170.9 (12.9)
Post-	141.5 (16.8)	135.4 (14.9)	138.6 (15.8)	131.4 (14.2)
Change	-31.0 (16.2)	-44.9 (16.6)	-36.6 (19.5)	-39.5 (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)

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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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	**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:** 6/50 pts withdrew from losartan 2/25 pts withdrew from enalapril **6) Specific adverse events:** **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

	Losartan (n = 50)	Enalapril (n = 25)
Adverse event	35 (70%)	19 (76%)

	Losartan (n = 50)	Enalapril (n = 25)
Headache	22%	20%
Dizziness	14%	12%
Edema	4%	12%
Cough	8%	12%

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Ruilope, Jager, and Prichard, 2001 **#4640**	**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:** - 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	**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%) **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%	**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:** 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 7 (4.1%) / 10 (6.1%) Fatigue 5 (2.9%) / 7 (4.3%) Diarrhea 5 (2.9%) / 3 (1.8%) Injury 4 (2.3%) / 2 (1.2%) Abdominal pain 3 (1.8%) / 4 (2.5%) Dizziness 3 (1.8%) / 5 (3.1%) Infection viral 2 (1.2%) / 5 (3.1%) Coughing 1 (0.6%) / 10 (6.1%) UTI 0 (0%) / 5 (3.1%)	**General comments:** None **Quality assessment:** Overall rating: Good Comments: Enalapril dose not comparable to eprosartan. **Applicability:** - Multinational, but virtually all Caucasian subjects

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		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 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 **#1860**	**Geographical location:** Japan (nationwide) **Study dates:** 2002 - Mar 2003 **Funding source:** Non-profit foundation, device manufacturers **Interventions:** CCB (n = 239) ACEI (n = 214)	**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	**1) Blood pressure:** Home values at 6 mo, measured using automated device: 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:	**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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (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>ARB (n = 200)

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>Median: NR
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)

SBP / DBP
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>CCB: 34% (82/239)
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>Comments:
- 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>Sato, Tabata, Hayashi, et al., 2003

#2640</td><td>Geographical location: Ibaraki, Japan

Study dates: NR

Funding source: NR

Interventions:
Cross sectional cohort of patients treated with:
- Trandolapril (n = 18)</td><td>Number of patients: 49 (cross-sectional cohort)

Age:
Mean (SD): 63.3
Median: NR
Range: NR

Sex (n [%]):
Female: 23 (47%)
Male: 26 (53%)</td><td>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</td><td>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</td></tr>
</table>

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- 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 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	**Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Seated BP measured using a mercury sphygmomanometer after 15-min rest (average of 3 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	**5) Safety:** NR **6) Specific adverse events:** ACEI: cough 2 patients No other clinical AEs observed **7) Persistence/adherence:** NR **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	- Cross-sectional without establishment of an inception cohort **Applicability:** - Limited to a single hospital in Japan - All patients had diabetic nephropathy stage 2 or 3A
Schieffer, Bunte, Witte, et al., 2004 **#12330**	**Geographical location:** Hanover and Hamburg, Germany **Study dates:** NR **Funding source:** Sanofi-Synthelabo **Interventions:**	**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);	**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	**General comments:** None **Quality assessment:** Overall rating: Poor Comments: - Not clear all patients were

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- 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 adequate?:** Yes (randomization list) **Baseline/run-in period:** NA **Duration of treatment:** 3 months **Duration of post-treatment followup:** NA	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 **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Enalapril / Irbesartan 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	**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:** Reported to be no difference between groups (no numerical data reported) **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	hypertensive - No run-in period - LV results not quantified **Applicability:** - Race of patients not described

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Hypotension (SBP < 90mm)		
Schram, van Ittersum, Spoelstra-de Man, et al., 2005 **#990**	**Geographical location:** 6 sites in 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 **Baseline/run-in period:** 1-mo run-in (patients treated with diet only); if on ACEIs, these were withdrawn for 3	**Number of patients:** - 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 **Recruitment setting:** Outpatient clinics, newspaper advertisements **Inclusion criteria:**	**1) Blood pressure:** 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:** No change (data not shown) **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate**	**General comments:** - 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. Direct comparator studies of ACEIs vs. ARBs (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>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</td><td>- 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</td><td>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])</td><td></td></tr>
<tr><td>Shand, 2000

#5660

and

Shand and Lynn, 2000

#12380</td><td>Geographical location:
Christchurch, New Zealand

Study dates: NR

Funding source: Merck Sharp and Dohme

Interventions:
- Losartan 50-100 mg daily (n = 15)
- 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</td><td>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)
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
<table><tr><th></th><th>Losartan</th><th>Enalapril</th></tr><tr><td>SBP</td><td>153 ± 18</td><td>141 ± 14</td></tr><tr><td>DBP</td><td>100 ± 13</td><td>96 ± 13</td></tr></table></td><td>1) Blood pressure:
Mean seated BP (SD):
<table><tr><th></th><th>Losart Pre-</th><th>Losart 120 days</th><th>Enal Pre-</th><th>Enal 120 days</th></tr><tr><td>SBP</td><td>153 (18)</td><td>138 (16)</td><td>141 (14)</td><td>134 (10)</td></tr><tr><td>DBP</td><td>100 (13)</td><td>88 (8)</td><td>96 (13)</td><td>87 (10)</td></tr></table>P < 0.01 for losartan SBP and DBP pre-/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)</td><td>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
- 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</td></tr>
</table>

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	meds; no other run-in **Duration of treatment:** 120 days **Duration of post-treatment followup:** NA	**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	**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) / 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 **#4460**	**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	**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	**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 / Amlodipine 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	**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

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (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: 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</td><td>Baseline blood pressure:
Supine pre-dialysis (only mean BP reported); measured using mercury sphygmomanometer

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</td><td>specified)

4) Morbidity: 1 MI (treatment group not specified)

5) Safety:
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):
<table><tr><th></th><th>Losartan</th><th>Enalapril</th><th>Amlodi-pine</th></tr><tr><td>Baseline</td><td>154.5 (9.9)</td><td>155.6 (14.3)</td><td>156.6 (7.3)</td></tr><tr><td>6 mo</td><td>114.6 (5.8)</td><td>135.3 (10.4)</td><td>137.2 (4.1)</td></tr><tr><td>Change</td><td>-24.7 (3.2)</td><td>-11.2 (4.1)</td><td>-10.5 (5.2)</td></tr></table>P < 0.05 for all pre-post for losart and enalapril, but not amlodipine
P< 0.05 for difference in losartan group compared to enalapril or amlodipine</td><td>to other studies
- Unique dialysis population; may not generalize to non-dialysis hypertensive patients</td></tr>
</table>

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (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>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>Tikkanen, Omvik, and Jensen, 1995

#7170

and

Nielsen, Dollerup, Nielsen, et al., 1997

#12180</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</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;</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 <</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. Direct comparator studies of ACEIs vs. ARBs (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>Duration of treatment: 12 wk

Duration of post-treatment followup: NA</td><td>average of 3 readings taken at 1-min intervals

<table>
<tr><th></th><th>Losartan</th><th>Enalapril</th></tr>
<tr><td>SBP</td><td>157.5 ±17.1</td><td>158.8 ± 16.5</td></tr>
<tr><td>DBP</td><td>103.1 ± 6.0</td><td>103.7 ± 6.1</td></tr>
</table>
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
- 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</td><td>0.05).

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

3) Mortality: NR

4) Morbidity: NR

5) Safety:
<table>
<tr><th></th><th>Losart, n (%)</th><th>Enal, n (%)</th><th>p-value</th></tr>
<tr><td>Total AEs</td><td>65 (32.2%)</td><td>93 (45.4%)</td><td>< 0.01</td></tr>
<tr><td>Possibly drug-related AEs</td><td>23 (11.4%)</td><td>52 (25.4%)</td><td>< 0.01</td></tr>
<tr><td>Withdrawals due to AEs</td><td>6 (3%)</td><td>14 (6.8%)</td><td>NS</td></tr>
<tr><td>Withdrawals due to drug-related AEs</td><td>3 (1.5%)</td><td>12 (5.9%)</td><td>< 0.05</td></tr>
</table>
6) Specific adverse events:
Headache, edema, rash/itching mentioned as AEs, but not quantified.
<table>
<tr><th></th><th>Losart</th><th>Enal</th><th>p-value</th></tr>
<tr><td>Dry cough at 12 wk</td><td>1%</td><td>12.2%</td><td>< 0.01</td></tr>
</table>
7) Persistence/adherence: NR

8) Lipid levels:
<table>
<tr><th></th><th>Losartan (mean change %)</th><th>Enalapril (mean change %)</th></tr>
<tr><td>Cholesterol level</td><td>1.8</td><td>-0.2</td></tr>
<tr><td>HDL cholesterol</td><td>2.1</td><td>1.5</td></tr>
<tr><td>Triglycerides</td><td>-3.0</td><td>2.3</td></tr>
</table></td><td></td></tr>
</table>

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (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>- 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</td><td>9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control:

<table><tr><td></td><td>Losartan (mean change %)</td><td>Enalapril (mean change %)</td></tr><tr><td>Glucose level</td><td>-0.8</td><td>0</td></tr></table>
11) LV mass/function: NR

12) Creatinine/GFR:

<table><tr><td></td><td>Losartan (mean change %)</td><td>Enalapril (mean change %)</td></tr><tr><td>Creatinine level</td><td>-0.1</td><td>1.7</td></tr></table>
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:

<table><tr><td></td><td>Losartan (n = 46)</td><td>Enalapril (n = 47)</td></tr><tr><td>Baseline</td><td>1.14 x/-2.48</td><td>0.95 x/-2.45</td></tr><tr><td>12 wks</td><td>0.81 x/-2.45</td><td>0.73 x/-2.0</td></tr></table>
Differences are significant pre-/post- (p < 0.05), but not between treatments.

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></td><td></td></tr>
</table>

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (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>Differences are significant pre-/posts (p < 0.05), but not between treatments.</td><td></td></tr>
<tr><td>Townsend, Haggert, Liss, et al., 1995

#7200</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 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</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%)
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</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>
<tr><td>≥ 65 yr</td><td>(25)</td><td>(30)</td><td></td></tr>
<tr><td>Wk 4</td><td>-9.0</td><td>-6.4</td><td>0.06</td></tr>
<tr><td>Wk 8</td><td>-9.6</td><td>-8.4</td><td>0.17</td></tr>
<tr><td>Wk 12</td><td>-12.7</td><td>-10.1</td><td>0.03</td></tr>
<tr><td>< 65 yr</td><td>(107)</td><td>(68)</td><td></td></tr>
<tr><td>Wk 4</td><td>-7.6</td><td>-4.9</td><td>0.19</td></tr>
<tr><td>Wk 8</td><td>-8.7</td><td>-8.6</td><td>0.06</td></tr>
<tr><td>Wk 12</td><td>-9.8</td><td>-8.6</td><td>0.75</td></tr>
</table>

2) Rate of use of a single antihypertensive agent for BP control:
Of 132 losartan patients, 62 (47%) received 50 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 mg enalapril, 39(29%) were titrated to and continued taking 10 mg enalapril, and 64(47%) received 10</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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		end of study	mg enalapril + 25 mg HCTZ by end of study. Between-group differences were not statistically significant.	
	Blinding: - Patients: Yes - Providers: NR - Assessors of outcomes: Yes	Baseline SiDBP: Losartan: 101 ± 5 Enalapril: 100 ± 4	**3) Mortality:** NR	
	Each patient got an active and a placebo of the alternative treatment using a double blind double dummy design	**Concurrent medications (n [%]):** NR	**4) Morbidity:** NR	
	Was allocation concealment adequate?: NR	**Comorbidities (n [%]):** NR	**5) Safety:** No lab test AEs were serious, no ECG AEs were serious	
	Baseline/run-in period: 4 week placebo run-in (2 placebo tablets each day in the morning, 1 matching losartan and 1 matching enalapril)	**Recruitment setting:** NR **Inclusion criteria:** Mean SDBP ≥ 95 and ≤ 115 mm, and did not vary by more than 7 mm between measurements	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	
	Duration of treatment: 12 weeks	**Exclusion criteria:** - Previously recd. ACE or ARBs - Sensitivity or intolerance to either drug - 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	No statistically significant difference in the number of patients who withdrew due to an AE (9 losartan vs. 12 enalapril)	
	Duration of post-treatment followup: NA		**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	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			11) LV mass/function: NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Uchiyama-Tanaka, Mori, Kishimoto, et al., 2005 **#1120**	**Geographical location:** Osaka, Japan **Study dates:** NR **Funding source:** NR **Interventions:** - Quinapril 10 mg (n = 25) - Losartan 50 mg (n = 18) 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	**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:** 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) / Losartan alone (n = 18) SBP 156 ± 14 / 156 ± 12 DBP 92 ± 9 / 92 ± 10 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]; n = 43 monotherapy responders):**	**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) 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 134 (43) / 121 (27)	**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 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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results			Comments/ quality/applicability
		History of smoking: 17 (39.5%) History of diabetes: 11 (26%) History of hyperlipidemia: (37%) **Recruitment setting:** Outpatients attending renal and 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	baseline LDL 1 yr HDL baseline HDL 1 yr TG baseline TG 1 yr	 126 (27) 56 (19) 59 (20) 147 (56) 150 (69)	 117 (31) 49 (13) 52 (16) 156 (73) 169 (55)	
		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)	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Cr reported in mg/dL None of the changes was statistically significant but no p-values reported **13) Proteinuria:** NR	
Verdecchia, Schillaci, Reboldi, et al., 2000 **#5560**	**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 **Duration of post-treatment followup:** NA	**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 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR	**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): Baseline / Followup / p-value Losartan 5.09 ± 0.79 / 5.23 ± 0.86 / NS Enalapril 5.51 ± 0.93 / 5.92 ± 0.92 / NS Mean HDL 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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Recruitment setting: - from PIUMA (Progetto Ipertensione Umbria Monitoaggio Ambulatoriale) study [ref 4, 14 in paper] **Inclusion criteria:** - Office SBP ≥ 140 and/or DBP ≥ 90 on ≥ 3 visits - ≥1 valid BP measurement within 24h before enrollment **Exclusion criteria:** - Previous antihypertensive therapy or drugs withdrawn from ≥ 4 wk - Evidence of CHF, CAD, significant valvular defects - Secondary causes of HTN - "Other concomitant important disease"	Mean LDL cholesterol (mmol/L): Losartan: Baseline 3.42 ± 0.79; Followup 3.32 ± 0.82; p-value NS Enalapril: Baseline 3.59 ± 0.85; Followup 3.77 ± 0.86; p-value NS Mean triglycerides (mmol/L): Losartan: Baseline 1.23 ± 0.49; Followup 1.34 ± 0.56; p-value NS Enalapril: Baseline 1.47 ± 0.78; Followup 1.78 ± 0.86; p-value NS **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** Mean glucose (mmol/L): Losartan: Baseline 5.36 ± 0.65; Followup 5.31 ± 0.61; p-value NS Enalapril: Baseline 5.56 ± 0.88; Followup 5.61 ± 0.90; p-value NS **11) LV mass/function:** LV mass (g/BSA [m^2]): Losartan: Baseline 98 ± 18; Followup 87 ± 19; p-value <0.001 Enalapril: Baseline 98 ± 20; Followup 89 ± 20; p-value <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): Losartan: Baseline 85.7 ± 10.4; Followup 83.9 ± 12.9; p-value NS Enalapril: Baseline 82.8 ± 14.7; Followup 93.2 ± 75.6; p-value NS Note - SD for enalapril on f/u must be a typo **13) Proteinuria:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Williams, Gosse, Lowe, et al., 2006 **#340**	**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 **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	**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) Median: NR Range: NR **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:** Seated trough BP measured in triplicate using a manual sphygmomanometer according to ASH guidelines |	Telmisartan	Ramipril
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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:**	**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% ($p = 0.004$) Also report BP in last 6 hours of 24 hours of ABPM **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** There were no deaths during the study. **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	**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. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- 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 using adequate contraception - Night shift workers	**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:** Compliance with treatment was high (> 98.8%) in both groups – recognize this is in 714/801 patients that completed study **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 **#12890**	**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	**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%	**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.	**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. Direct comparator studies of ACEIs vs. ARBs (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:** NA **Duration of post-treatment followup:** 1 yr	**Race/ethnicity (n [%]):** NR; database stated to be "demographically diverse" **Baseline blood pressure:** NR **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, including drug-insured lives from health care insurance carriers, managed care organizations, employers, and retirement and government plans."	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. 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. 1-yr persistence / Compliance 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. Direct comparator studies of ACEIs vs. ARBs (continued)

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

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, in italics, 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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

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.*

Klein IH, Ligtenberg G, Oey PL, et al. Enalapril and losartan reduce sympathetic hyperactivity in patients with chronic renal failure. J Am Soc Nephrol 2003;14(2):425-30. *Exclude: Followup < 12 wk.*

Kraiczi H, Hedner J, Peker Y, et al. Comparison of atenolol, amlodipine, enalapril, hydrochlorothiazide, and losartan for antihypertensive treatment in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2000;161(5):1423-8. *Exclude: Followup < 12 wk.*

Lacourciere Y. The incidence of cough: a comparison of lisinopril, placebo and telmisartan, a novel angiotensin II antagonist. Telmisartan Cough Study Group. Int J Clin Pract 1999;53(2):99-103. *Exclude: Followup < 12 wk.*

Lacourciere Y. A multicenter, randomized, double-blind study of the antihypertensive efficacy and tolerability of irbesartan in patients aged > or = 65 years with mild to moderate hypertension. Clin Ther 2000;22(10):1213-24. *Exclude: Followup < 12 wk.*

Lacourciere Y, Brunner H, Irwin R, et al. Effects of modulators of the renin-angiotensin-aldosterone system on cough. Losartan Cough Study Group. J Hypertens 1994;12(12):1387-93. *Exclude: Followup < 12 wk.*

Lacourciere Y, Lefebvre J. Modulation of the renin-angiotensin-aldosterone system and cough. Can J Cardiol 1995;11 Suppl F:33F-9F. *Exclude: Followup < 12 wk.*

Lee C-M, Lee Y-T, Lang MG, et al. A comparison of valsartan and captopril in Taiwanese patients with essential hypertension. Adv Ther 1999;16(1):39-48. *Exclude: Followup < 12 wk.*

Lee YJ, Chiang YF, Tsai JC. Severe nonproductive cough and cough-induced stress urinary incontinence in diabetic postmenopausal women treated with ACE inhibitor. Diabetes Care 2000;23(3):427-8. *Exclude: Followup < 12 wk.*

Leu HB, Charng MJ, Ding PY. A double blind randomized trial to compare the effects of eprosartan and enalapril on blood pressure, platelets, and endothelium function in patients with essential hypertension. Jpn Heart J 2004;45(4):623-35. *Exclude: Followup < 12 wk.*

Li-Saw-Hee FL, Beevers DG, Lip GY. Effect of antihypertensive therapy using enalapril or losartan on haemostatic markers in essential hypertension: a pilot prospective randomised double-blind parallel group trial. Int J Cardiol 2001;78(3):241-6. *Exclude: Followup < 12 wk.*

Mahmud A, Feely J. Favourable effects on arterial wave reflection and pulse pressure amplification of adding angiotensin II receptor blockade in resistant hypertension. J Hum Hypertens 2000;14(9):541-6. *Exclude: Followup < 12 wk.*

Mahmud A, Feely J. Reduction in arterial stiffness with angiotensin II antagonist is comparable with and additive to ACE inhibition. Am J Hypertens 2002;15(4 Pt 1):321-5. *Exclude: Followup < 12 wk.*

Mallion J-M, Boutelant S, Chabaux P, et al. Valsartan, a new angiotensin II antagonist blood pressure reduction in essential hypertension compared with an angiotensin converting enzyme inhibitor, enalapril. Blood Press Monit 1997;2(3-4):179-84. *Exclude: Could not obtain copy.*

Matsumoto T, Minai K, Horie H, et al. Angiotensin-converting enzyme inhibition but not angiotensin II type 1 receptor antagonism augments coronary release of tissue plasminogen activator in hypertensive patients. J Am Coll Cardiol 2003;41(8):1373-9. *Exclude: Followup < 12 wk.*

Morgan T, Anderson A. Low-dose combination therapy with perindopril and indapamide compared with irbesartan. Clinical Drug Investigation 2002;22(8):553-60. *Exclude: Not ACEI vs. ARB.*

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