

Drug Class Review

Direct Renin Inhibitors, Angiotensin Converting Enzyme Inhibitors, and Angiotensin II Receptor Blockers

Final Report

January 2010

The Agency for Healthcare Research and Quality has not yet seen or approved this report

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Susan Norris, MD, MPH
Jessica Weinstein, MD
Kimberly Peterson, MS
Sujata Thakurta, MPA:HA

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

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TABLE OF CONTENTS

INTRODUCTION	7
Purpose and Limitations of Systematic Reviews	9
Scope and Key Questions	12
METHODS	13
Inclusion Criteria	13
Literature Search	15
Study Selection	16
Data Abstraction	16
Validity Assessment	16
Data Synthesis	17
Peer Review	17
Public Comment	18
RESULTS	18
Overview	18
Coronary Heart Disease, Heart Failure, and Left Ventricular Dysfunction	20
Summary of findings	20
Detailed assessment	23
Aliskiren compared with placebo (combination therapy) (n=1)	23
Candesartan compared with enalapril (monotherapy and combination therapy) (n=1)	24
Irbesartan compared with ramipril (monotherapy combined with diuretic) (n=1)	24
Losartan compared with captopril (monotherapy) (n=3)	24
Harms	26
Subgroup analyses	26
Losartan compared with enalapril (monotherapy and combination therapy) (n=5)	26
Subgroups	27
Telmisartan compared with enalapril (monotherapy plus diuretic) (n=1)	27
Telmisartan compared with ramipril (monotherapy and combination therapy) (n=1)	27
Harms	28
Subpopulations	28
Valsartan compared with captopril (monotherapy and combination therapy) (n=1)	28
Harms	29
Subpopulations	29
Valsartan compared with enalapril (monotherapy)	29
Subpopulations	29
Hypertension	36
Summary of findings	36
Detailed assessment	38
Comparison of monotherapies	38
Losartan	38
Losartan compared with enalapril	38
Losartan compared with captopril, fosinopril, perindopril, quinapril, and ramipril	39
Candesartan	40
Candesartan compared with enalapril	40
Candesartan compared with lisinopril and perindopril	40
Valsartan	41
Valsartan compared with benazepril, lisinopril, and ramipril	41
Eprosartan	42
Eprosartan compared with enalapril	42
Telmisartan	43
Telmisartan compared with enalapril and ramipril	43

Comparison of combination therapy with an AIIRA plus an ACE-I to AIIRA and ACE-I monotherapies in adults with hypertension.....	44
Effectiveness/efficacy outcomes	45
Harms	45
Subgroups.....	45
Nondiabetic Chronic Kidney Disease	45
Summary of findings.....	45
Detailed assessment.....	49
Monotherapy: Inter-class comparison of effectiveness, efficacy, and harms between AIIRA and ACE-I.....	49
Proteinuric chronic kidney disease	49
Losartan.....	50
Losartan compared with lisinopril.....	50
Losartan compared with enalapril	50
Losartan compared with benazepril	51
Losartan compared with trandolapril.....	53
Losartan compared with perindopril	53
Candesartan	53
Candesartan compared with lisinopril	53
Candesartan compared with perindopril and trandolapril	54
Valsartan.....	54
Valsartan compared with lisinopril.....	54
Valsartan compared with benazepril	55
Valsartan compared with ramipril.....	56
Telmisartan	57
Telmisartan compared with enalapril.....	57
Irbesartan.....	57
Irbesartan compared with fosinopril	57
Combination therapy: Inter-class comparison of effectiveness, efficacy and harms between AIIRA and ACE-I.....	58
Proteinuric Chronic Kidney Disease	58
Monotherapy with ACE-I and AIIRA compared with combination therapy.....	60
Losartan	60
Losartan in combination with lisinopril	60
Losartan in combination with enalapril	60
Losartan in combination with benazepril	61
Candesartan.....	61
Candesartan in combination with lisinopril	61
Valsartan	62
Valsartan in combination with benazepril	62
Valsartan in combination with ramipril	63
Irbesartan	63
Irbesartan in combination with fosinopril	63
Combination therapy with ACE-I and AIIRA compared with monotherapy with ACE-I or AIIRA	63
ACE-I and AIIRA compared with ACE-I alone	63
Losartan and lisinopril compared with lisinopril alone	63
Candesartan and ramipril compared with ramipril alone	64
Irbesartan and ramipril compared with ramipril alone.....	65
ACE-I and AIIRA compared with AIIRA alone	65
Candesartan and benazepril compared with candesartan alone	65
Valsartan and benazepril compared with valsartan alone.....	66
Diabetic Nephropathy	67
Summary of findings.....	67
Detailed assessment.....	69
Aliskiren used in combination with an AIIRA or an ACE-I.....	69
Effectiveness/efficacy	70

Harms	70
Subgroups.....	70
Comparison of AIIRA and ACE-I monotherapies in adults with diabetic nephropathy	70
Telmisartan	71
Telmisartan compared with enalapril	71
Losartan	71
Losartan compared with enalapril.....	71
Losartan compared with quinapril.....	73
Candesartan.....	74
Candesartan compared with lisinopril.....	74
Candesartan compared with ramipril.....	74
Valsartan	75
Valsartan compared with enalapril	75
Valsartan compared with benazepril	75
Irbesartan	76
Irbesartan compared with perindopril	76
Comparison of combination therapy with an AIIRA plus an ACE-I to monotherapy with an AIIRA and/or an ACE-I.....	76
Combination therapy with losartan plus enalapril	77
Combination therapy with candesartan plus an ACE-I	78
Candesartan plus lisinopril.....	78
Candesartan plus ramipril.....	78
Combination therapy with irbesartan plus enalapril	79
Combination therapy with valsartan plus benazepril	79
Serious Harms in Observational Studies: All Populations.....	80
Summary of findings.....	80
Detailed assessment	81
Withdrawal rates	81
Adverse events	82
Serious renal adverse events	82
Serious cardiovascular adverse events.....	82
Deaths.....	83
Other serious adverse events.....	83
Adverse events in subpopulations.....	83
CONCLUSIONS AND LIMITATIONS.....	90
SUMMARY	90
REFERENCES	106
 TABLES	
Table 1. Included drugs.....	8
Table 2. DRI, ACE-I, and AIIRA drugs available in the United States or in Canada	14
Table 3. Randomized controlled trials comparing ACE-I and AIIRA in populations with heart disease ..	23
Table 4. AIIRA drugs compared with ACE-I drugs in populations with heart failure or cardiovascular disease	30
Table 5. Comparison of eprosartan and enalapril on cough-related adverse events	43
Table 6. Observational studies of ACE-I and AIIRA drugs.....	84
Table 7. Summary of the evidence ^a	90

FIGURES

Figure 1. Results of literature search 19

APPENDIXES

Appendix A. Glossary 117
Appendix B: Search strategies 129
Appendix C. Methods used to assess quality of studies 133
Appendix D. Excluded trials..... 137
Appendix E. Black box warnings for included drugs 144

EVIDENCE TABLES

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JM Wright MD, PhD
University of British Columbia

Raghav Wusirika, MD
Oregon Health and Science University

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INTRODUCTION

The renin-angiotensin system is a complex biologic system between the heart, brain, blood vessels, and kidneys that leads to the production of biologically active agents, including angiotensin I and II and aldosterone, which act together to impact a variety of bodily functions including blood vessel tone, sodium balance, and glomerular filtration pressure. The multiple and varied effects of these agents allows the renin-angiotensin system to play a wide role in the pathology of hypertension, cardiovascular health, and renal function.

Our ability to begin to intervene upon the complex cycle of hormone and other biochemical agent production within the renin-angiotensin system began with the advent of the first orally active ACE-I (angiotensin converting enzyme inhibitor), captopril, in 1981. ACE-Is interrupt the cycle within the renin-angiotensin system by blocking the conversion of angiotensin I to angiotensin II.¹ Trials subsequent to the development of oral ACE-I agents demonstrated the broad impact of ACE-I inhibition. Inhibition of the renin-angiotensin system via ACE-I agents has now been found to be not only effective in the control of hypertension,² but also reduces the risk of acute myocardial infarction among patients with heart failure,³ left ventricular remodeling after acute myocardial infarction,⁴ mortality among patients with severe heart failure and reduced left ventricular ejection fraction,^{5,6} and progression of renal disease among diabetic and non-diabetic patients.⁷⁻¹⁰ While use of ACE-I inhibitors does diminish the amount of angiotensin II in circulation, it also leads to an increase in bradykinin, which is felt to be the etiology of some ACE-I-unique adverse effects such as cough.

AIIRAs (angiotensin II receptor blockers) were developed as an alternative to ACE-I, and block the interaction between angiotensin II and the angiotensin receptor. Losartan, the first commercially available AIIRA, was approved for clinical use in 1995. These agents offer benefits to ACE-Is with interruption of the renin-angiotensin system, but without an increase in bradykinin. The advent of AIIRAs resulted in a new option for those who could not tolerate ACE-I agents, and were found to yield similar results in terms of impact on hypertension, cardiovascular disease and heart failure, as well as renal disease progression.¹¹⁻¹⁴ A newer type of agent, a DRI (direct renin inhibitor), has recently become available and may also be found to similarly impact these illnesses. Limited trial data are now available for these agents.

The strength of the evidence in support of renin-angiotensin system blockade has led to incorporation of ACE-Is and AIIRAs into important clinical guidelines. The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) currently recommends an ACE-I or AIIRA as first line options for patients with stage 1 hypertension who have diabetes, chronic kidney disease, history of stroke or myocardial infarction, or high cardiovascular risk.¹⁵ The American Diabetes Association similarly recommends use of an ACE-I or AIIRA for diabetic patients with hypertension or diabetic nephropathy.¹⁶ That recommendation is echoed by the Kidney Disease Outcome Quality Initiative guidelines, which recommend ACE-Is or AIIRAs for patients with diabetic or non-diabetic proteinuric renal disease.¹⁷

Currently 11 ACE-Is, 7 AIIRAs, and 1 DRI are available in the United States and Canada (Table 1).

Table 1. Included drugs

Active ingredient Dosage form	Trade name	Formulations ^a	Daily maintenance dosage ^a	Indications approved by the US Food and Drug Administration
Direct renin inhibitor (DRI)				
Aliskiren Oral Tablet	Tekturna [®] , Rasilez ^{®b}	EQ 150-300 mg base	150-300 mg in 1 dose	1) Hypertension
Angiotensin converting enzyme inhibitor (ACE-I)				
Benazepril Oral Tablet	Lotensin [®]	5-40 mg	10-80 mg in 1 or 2 doses	1) Hypertension
Captopril Oral Tablet	Capoten [®]	12.5-100 mg	12.5-150 mg in 2 or 3 doses	1) Hypertension 2) Congestive heart failure 3) Myocardial infarction 4) Diabetic nephropathy
Cilazapril ^b Oral Tablet	Inhibace [®]	1-5 mg	2.5-10 mg in 1 or 2 doses	1) Hypertension 2) Congestive heart failure
Enalapril Oral Tablet	Vasotec [®]	2.5-20 mg	2.5-40 mg in 1 or 2 doses	1) Hypertension 2) Congestive heart failure
Fosinopril Oral Tablet	Monopril [®]	10-40 mg	10-80 mg in 1 or 2 doses	1) Hypertension 2) Heart failure
Lisinopril Oral Tablet	Prinivil [®] , Zestril [®]	2.5-40 mg	5-40 mg in 1 dose	1) Hypertension 2) Heart failure 3) Acute myocardial infarction
Moexipril ^c Oral Tablet	Univasc [®]	7.5-15 mg	7.5-30 mg 1 or 2 doses	1) Hypertension
Perindopril Oral Tablet	Aceon [®] , Coversyl ^{®b}	2-8 mg	4-8 mg in 1 or 2 doses	1) Stable coronary artery disease 2) Hypertension 3) Congestive heart failure ^d 4) The reduction of cardiovascular risk in patients with hypertension or post-myocardial infarction and stable coronary disease ^d
Quinapril Oral Tablet	Accupril [®]	5-40 mg	5-80 mg in 1 or 2 doses	1) Hypertension 2) Congestive heart failure
Ramipril Oral Tablet, Oral Capsule	Altace [®]	1.25-10 mg	1.25-20 mg in 1 or 2 doses	1) Reduction in the risk of myocardial infarction, stroke, death from cardiovascular causes 2) Hypertension 3) Heart failure post

Active ingredient Dosage form	Trade name	Formulations ^a	Daily maintenance dosage ^a	Indications approved by the US Food and Drug Administration
Trandolapril Oral Tablet	Mavik [®]	1-4 mg	1-8 mg in 1 or 2 doses	myocardial infarction 1) Hypertension 2) Heart failure post myocardial infarction, or left ventricular dysfunction post myocardial infarction
Angiotensin II receptor blocker (AIIRA)				
Candesartan Oral tablet	Atacand [®]	4-32 mg	8-32 mg in 1 dose	1) Hypertension 2) Heart failure
Eprosartan Oral Tablet	Teveten [®]	EQ 400-600 mg base	400-800 mg in 1 or 2 doses	1) Hypertension
Irbesartan Oral Tablet	Avapro [®]	75-300 mg	150-300 mg in 1 dose	1) Hypertension 2) Nephropathy in type 2 diabetes patients
Losartan Oral Tablet	Cozaar [®]	25-100 mg	25-100 mg in 1 or 2 doses	1) Hypertension 2) Hypertensive patients with left ventricular hypertrophy 3) Diabetic nephropathy
Olmesartan Oral Tablet	Benicar [®] Olmotec ^{®b}	5-40 mg	20-40 mg in 1 dose	1) Hypertension
Telmisartan Oral Tablet	Micardis [®]	20-80 mg	40-80 mg in 1 dose	1) Hypertension
Valsartan Oral Tablet	Diovan [®]	40-320 mg	80-320 mg in 1 dose	1) Hypertension 2) Heart failure 3) Post myocardial infarction

Abbreviations: bid, twice daily; tid, 3 times daily; qd, once daily.

^a Obtained from the *Medical Letter*.

^b Only available in Canada.

^c Not available in Canada.

^d Indications for Coversyl only.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the “average” patient than results from the highly selected populations in

efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of studies' results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The goal of this report is to compare the effectiveness and harms between aliskiren and placebo and between AIIRAs and ACEIs in the treatment of diagnosed coronary heart disease, hypertension, left ventricular dysfunction, heart failure, nondiabetic chronic kidney disease, or diabetic nephropathy. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and, based on these, eligibility criteria for studies. A draft of these questions and inclusion and exclusion criteria were posted on the Drug Effectiveness Review Project website for public comment. Then, a group of clinicians specializing in nephrology and hypertension were consulted for clinical insight into the proposed key questions. The draft was reviewed and revised by representatives of the organizations participating in the Drug Effectiveness Review Project. Revision took into consideration input from the public, clinical advisors, and the organizations' desire for the key questions to reflect populations, drugs, and outcome measures of interest to clinicians and patients. These organizations approved the following key questions to guide the review for this report:

1. For adults with diagnosed coronary heart disease, hypertension, left ventricular dysfunction, heart failure, nondiabetic chronic kidney disease, or diabetic nephropathy, what is the effectiveness and efficacy and what are the harms of aliskiren compared with placebo?
 - 1a. When used as monotherapy?
 - 1b. When used in combination with angiotensin converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (AIIRA) drugs?
2. For adults with diagnosed coronary heart disease, hypertension, left ventricular dysfunction, heart failure, nondiabetic chronic kidney disease, or diabetic nephropathy, what are the inter-class differences in effectiveness and efficacy between direct renin inhibitor (DRI), ACE-I and AIIRA drugs?
 - 2a. When used as monotherapy?
 - 2b. When used in combination with one another?
3. For adults with diagnosed coronary heart disease, hypertension, left ventricular dysfunction, heart failure, nondiabetic chronic kidney disease, or diabetic nephropathy, what are the inter-class differences in harms between DRI, ACE-I and AIIRA drugs?
4. Are there subgroups based on demographics (age, racial groups, gender), other medications, or co-morbidities for which there are inter-class differences between DRI, ACE-I and AIIRA drugs?

METHODS

Inclusion Criteria

Populations

Adults with any of the following indications:

- Diagnosed coronary heart disease (including post-myocardial infarction)
- Hypertension
- Left ventricular dysfunction
- Heart failure
- Nondiabetic chronic kidney disease, with or without proteinuria
- Diabetic nephropathy, defined as documented diabetes, with either microalbuminuria or macroalbuminuria, and any level of renal function. Trials of diabetics with normo albuminuria will be excluded.

Excluded:

- Renal transplantation

We defined microalbuminuria as an albuminuria level by timed collections of 20 to 200 micrograms per minute,¹⁸ 30-300 milligrams/24 hours,^{19, 20} or a proteinuria level via spot protein to creatinine ratio of 30- 300 milligrams protein/gram creatinine.^{19, 20} We defined overt proteinuria (or macroalbuminuria) as proteinuria greater than 300 mg /24 hours on timed collection, or greater than 0.15 milligram protein per milligram creatinine on spot value.²⁰ We defined abnormal renal function as an elevated creatinine or an estimated glomerular filtration rate below 60 ml/min/1.73 m² or an abnormal creatinine clearance.²⁰

Drugs

Table 2 lists the drugs included in this report.

Table 2. DRI, ACE-I, and AIIRA drugs available in the United States or in Canada

Drug type	Active ingredient	Drug name
Direct renin inhibitor (DRI)	Aliskiren	Tekturna, Rasilez ^a
	Benazepril	Lotensin
Angiotensin-converting enzyme inhibitor (ACE-I)	Captopril	Capoten
	Cilazapril ^a	Inhibace
	Enalapril	Vasotec
	Fosinopril	Monopril
	Lisinopril	Prinivil, Zestril
	Moexipril ^b	Univasc
	Quinapril	Accupril
	Ramipril	Altace
	Perindopril	Aceon, Coversyl ^a
	Trandolapril	Mavik
	Angiotensin II receptor blocker (AIIRA)	Losartan
Telmisartan		Micardis
Candesartan		Atacand
Eprosartan		Teveten
Irbesartan		Avapro
Olmesartan ^b		Benicar
Valsartan		Diovan

^a Only available in Canada.

^b Not available in Canada.

Effectiveness and efficacy outcomes

- All-cause mortality, cardiovascular mortality, sudden death
- Cardiovascular events (stroke, myocardial infarction, or death or hospitalization due to heart failure)
- Chronic kidney disease, end-stage renal disease, dialysis, transplantation
- Changes in renal function, including serum creatinine, estimated glomerular filtration rate, proteinuria and albuminuria (total amount over a 24-hour period, but not solely short-term excretion rates per minute or per hour), creatinine clearance
- Quality of life
- Symptomatic improvement in heart failure symptoms (heart failure class, functional status, visual analogue scores, exercise tolerance tests with symptom outcomes)
- Cardiovascular hospitalizations
- Overall withdrawals

Harms

- Numbers of adults who experienced the following:
 - One or more adverse event
 - One or more serious adverse event (life threatening or requiring medical intervention, including hospitalization)
- Total withdrawals due to any adverse event
- Specific harms (including, but not limited to hypotension, hyperkalemia, acute kidney injury, cough, angioedema, gastrointestinal effects) or withdrawals due to specific harms
- Harms considered to be major are defined as those that required unanticipated and/or urgent medical treatment (including, but not limited to hypotension, hyperkalemia, acute kidney injury, angioedema)

Study designs

Effectiveness/efficacy outcomes

1. Randomized controlled trials, controlled clinical trials, and good-quality systematic reviews that:
 - a. Compared aliskiren to placebo
 - b. Made direct inter-class comparisons between individual DRI, ACE-I and AIIRA drugs. Trials that assume a class effect and only provide a comparison to a treatment group consisting of multiple AIIRAs or multiple ACE-Is (trials that don't stratify by individual AIIRAs or ACE-Is) will be excluded.

Harms

1. Randomized controlled trials, controlled clinical trials, and good-quality systematic reviews included for effectiveness/efficacy outcomes that:
 - a. Compared aliskiren to placebo
 - b. Made direct inter-class comparisons between DRI, ACE-I and AIIRA drugs.
2. Large single-group or multi-group population-based cohort ($N \geq 1000$) or case-control ($N \geq 500$ cases) studies that evaluated major harms. If studies with these sample sizes were not identified studies of $N \geq 200$ were considered.

Literature Search

We searched Ovid MEDLINE[®] (1950-June week 2, 2009), the Cochrane Database of Systematic Reviews[®] (2nd Quarter 2009), and the Cochrane Central Register of Controlled Trials[®] (2nd Quarter, 2009) using included drugs, indications, and study designs as search terms. (See Appendix B for complete search strategies). We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration's Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote[®] XI, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form were not included because inadequate details were available for quality assessment.

Data Abstraction

The following data were abstracted from included trials: study design; setting; population characteristics, including sex, age, ethnicity, and diagnosis; eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intention-to-treat results. In cases where only per protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available. Data abstraction was performed by one reviewer and independently checked by a second reviewer.

For the body of evidence in adults with hypertension, complete data abstraction for the majority of trials was publicly available in a good-quality systematic review completed by the Duke Evidence-based Practice Center in November, 2007.^{21, 22}

(<http://www.effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=12%20&DocID=48>). We therefore only completed *de novo* data abstraction for additional trials that we identified.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix C. These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria.^{23, 24} We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. 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 *likely* to be valid, while others are only *possibly* valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. Quality assessment of all trials was independently performed by 1 reviewer. Disagreements were resolved by consensus. We did not rate the quality of observational studies.

For the trials of adults with hypertension for which quality assessments were previously completed by the Duke Evidence-based Practice Center (<http://www.effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=12%20&DocID=48>), *de novo* quality assessment was initially independently performed by one Oregon Evidence-based Practice Center reviewer (K.P.). Only in cases where there was a disagreement between the quality assessment of the initial Oregon Evidence-based Practice Center reviewer and the Duke Evidence-based Practice Center, was a second independent quality assessment completed (L.H.).

Included systematic reviews were also rated for quality (see Appendix C). We rated the internal validity based on a clear statement of the questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies. Again, these studies were categorized as good when all criteria were met.

The overall strength of evidence for a body of evidence for each key question and outcome reflects the risk of bias of the studies (based on quality and study designs), consistency of results, directness of the evidence, and the precision of pooled estimates.²⁵ Strength of evidence was graded as very low, low, moderate, or high. In order to simplify our approach for this review, we did not grade bodies of evidence in which only a single study was available and “Strength of Evidence” grades are listed as “not applicable” in the Summary of Evidence (Table 7).

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Both in the Evidence Tables and throughout the report, for all creatinine levels reported in units of micromole/L, we converted to units of mg/dL by dividing by 88.4.

As there were no occasions in which a particular outcome was reported by a sufficient number of studies that were homogeneous enough that combining their results could be justified, no quantitative analyses were conducted using meta-analyses in this review. Therefore, the data were summarized only qualitatively throughout the report.

We define statistical significance as $\alpha=0.05$.

Peer Review

We requested and received peer review of the report from 3 experts. Their comments were reviewed and, where possible, incorporated into the final document. All comments and the authors’ proposed actions were reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of the report. Names of peer reviewers for the Drug Effectiveness Review Project are listed at www.ohsu.edu/drugeffectiveness.

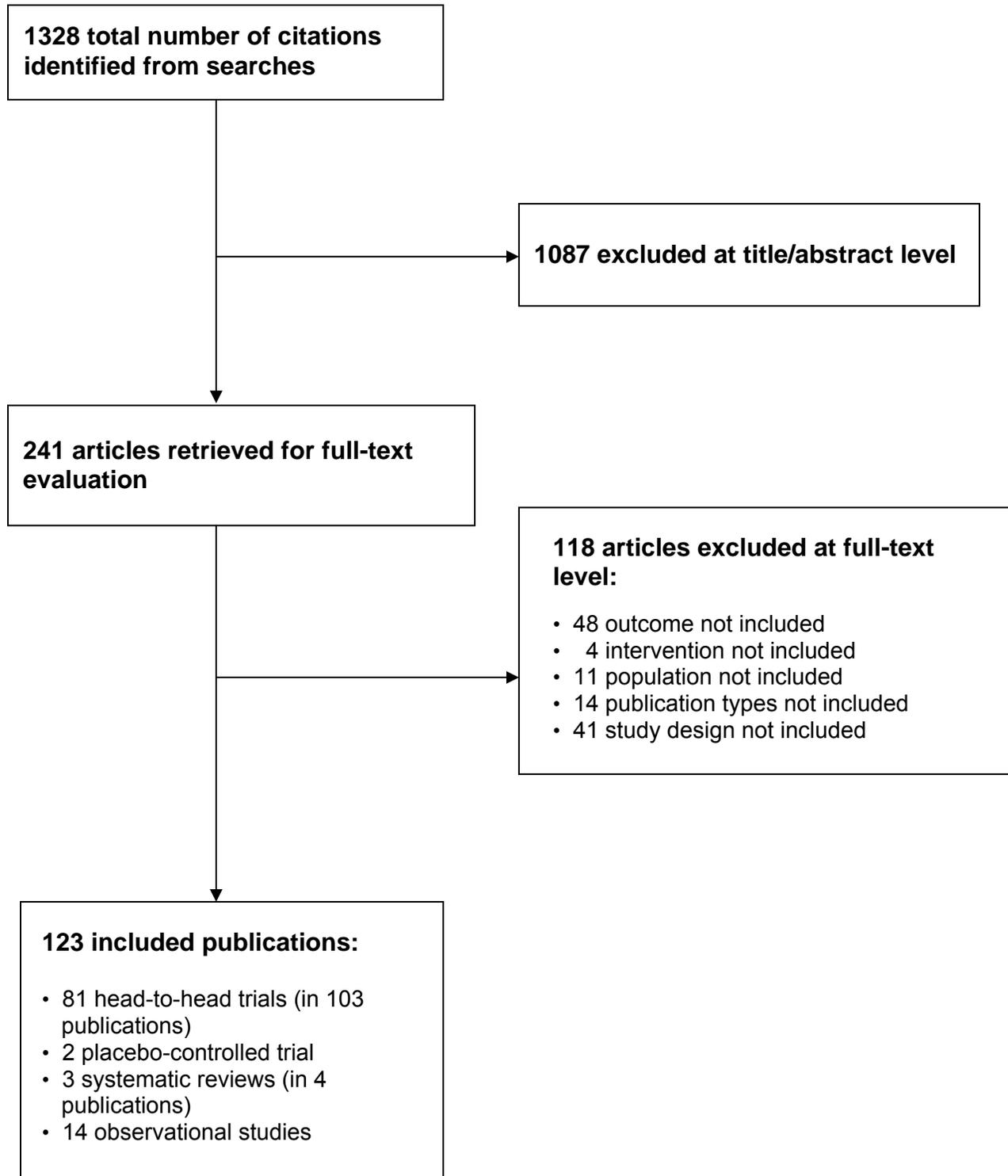
Public Comment

This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 3 pharmaceutical companies.

RESULTS

Overview

Literature searches identified 1328 citations. We received dossiers from the manufacturers of aliskiren, irbesartan, olmesartan, telmisartan, and valsartan. The results of the study selection process are outlined in Figure 1. See Appendix D for the list of studies that were excluded at the full-text level and the reasons for their exclusion.

Figure 1. Results of literature search

Coronary Heart Disease, Heart Failure, and Left Ventricular Dysfunction

Summary of findings

- Fourteen trials compared ACE-Is to AIIRAs, either as monotherapy or combination therapy.
- One trial compared aliskiren to placebo added to an ACE-I or an ARB (angiotensin receptor blocker).
- The majority of trials were of fair quality, while 3 were rated of good quality, and 2 poor quality.

Aliskiren compared with placebo (combination therapy) (n=1)

- In a trial (N=302) of patients with heart failure and hypertension on an ACE-I or an ARB, there was no significant difference between aliskiren and placebo in serum creatinine, overall withdrawals, withdrawals due to adverse events, or individual adverse events.

Candesartan compared with enalapril (monotherapy and combination therapy) (n=1)

- In the RESOLVD trial (N=768, fair quality) at 43-week follow-up, there were no statistically significant differences between treatment with captopril, enalapril, and the combination of the 2 drugs for the 6-minute walk test; New York Heart Association classification; rates of death, heart failure, or other hospitalizations; quality of life; renal dysfunction; or symptomatic hypotension. This trial was stopped early and was not powered for mortality and morbidity.

Irbesartan compared with ramipril (monotherapy combined with diuretic) (n=1)

- In a small, fair-quality trial (N=150), at 52-week follow-up, there were no significant differences in quality of life, deaths, or rates of hospitalization in patients on diuretics alone, diuretics plus irbesartan, or diuretics plus ramipril.

Losartan compared with captopril (monotherapy) (n=3)

- Three large, international trials examined this comparison.
- In ELITE, a fair-quality trial with 48-week follow-up (N=722), death and/or heart failure admissions were decreased with losartan ($P=0.075$). This reduction was primarily due to a decrease in all-cause mortality with losartan ($P=0.035$), which was mainly due to a decrease in sudden cardiac deaths. There was no significant difference among treatment groups in patients with heart failure for the primary composite endpoint of renal dysfunction, nor was there a significant difference in quality of life or admissions for heart failure.
- In ELITE II, also of fair quality (N=3152), there was no significant difference in any outcome, including all-cause mortality (the primary endpoint), sudden death or resuscitated arrest, total hospital admissions, admissions for heart failure, or health related quality of life at median follow-up of 1.5 years.
- In OPTIMAL, a good-quality trial (N=5477), in patients with an acute myocardial infarction and heart failure there was no difference between losartan and captopril for the

primary outcome of all-cause mortality at median follow-up of 2.7 years, nor were there significant differences between groups for sudden death, fatal or non-fatal reinfarction, and hospital admissions. Cardiovascular death was more common with losartan than captopril ($P=0.032$).

- In all 3 trials, losartan was better tolerated than captopril, as indicated by lower rates of total withdrawals, fewer withdrawals due to adverse events, and lower rates of cough and angioedema.

Losartan compared with enalapril (monotherapy and combination therapy) (n=5)

- Five small trials compared losartan with enalapril, all in populations with stable heart failure. Follow-up was short term: 8 weeks to 6 months. All studies examined monotherapy, except 1. Three of these studies were of fair quality and 2 were of poor quality.
- Monotherapy
 - Exercise capacity (2 studies) improved in both monotherapy groups with no significant difference between groups.
 - Symptoms were variably affected (2 studies), with no significant differences between treatment groups.
- Combination therapy
 - Quality of life improved slightly with enalapril and lisinopril monotherapy compared with placebo ($P>0.05$), with no significant further improvement with the 2 drugs in combination.
- These trials provided few data on adverse events and subpopulations.

Telmisartan compared with enalapril (monotherapy combined with a diuretic) (n=1)

- There were no significant differences within or between treatments with continuation of enalapril compared with switching to various telmisartan dosages, all combined with a diuretic, at 12 weeks of follow-up patients on the outcomes of exercise duration, New York Heart Association classification, or quality of life.
- Adverse event rates including cough were similar between telmisartan and enalapril.

Telmisartan compared with ramipril (monotherapy and combination therapy) (n=1)

- ONTARGET, a good-quality trial, examined both monotherapy and combination of patients with vascular disease, with median follow-up of 56 months.
- Monotherapy
 - Telmisartan was not inferior to ramipril for the prespecified, composite primary outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Results were consistent across all components of the primary outcome.
 - Telmisartan was not inferior to ramipril for the secondary outcomes, including the composite of death from cardiovascular causes, myocardial infarction, or stroke; deaths; revascularization; hospitalization for angina; worsening or new angina; new diagnosis of diabetes; or heart failure.
 - For the primary renal composite outcome of dialysis, doubling of serum creatinine, and death, event rates were similar between the 2 monotherapies.

- More subjects stopped telmisartan due to hypotension symptoms than ramipril.
- Combination therapy
 - Telmisartan combined with ramipril was not significantly better than ramipril alone for the primary outcome, with no significant differences also noted for the secondary outcomes listed above.
 - For the primary renal composite outcome, event rates were increased with combination therapy ($P=0.037$).
 - More subjects permanently discontinued ramipril as monotherapy or combination therapy because of cough or angioedema than telmisartan monotherapy.
 - Discontinuation due to hypotension, syncope, diarrhea, or renal impairment was more likely to occur with combination therapy than with ramipril monotherapy ($P<0.05$).
 - For the primary composite outcome, results were similar between ramipril and telmisartan or combination therapy for subgroups based on cardiovascular disease, systolic blood pressure, diabetes, age, or sex.

Valsartan compared with captopril (monotherapy and combination therapy) (n=1)

- VALIANT, a good-quality trial, examined patients with an acute myocardial infarction complicated by heart failure and/or left ventricular systolic dysfunction during median follow-up of 24.7 months.
- Monotherapy
 - There was no significant difference in death rates, quality of life, and hospitalization rates between the valsartan and captopril groups.
 - Valsartan was not inferior to captopril for mortality ($P=0.004$) and for the composite endpoint of fatal and nonfatal cardiovascular events ($P<0.001$).
 - Therapy discontinuation due to hypotension was more common with valsartan ($P<0.05$), while discontinuation due to cough was more common with captopril ($P<0.05$).
- Combination therapy
 - There was no significant difference in death rates and quality of life between combination therapy and captopril monotherapy.
 - Percentage of patients not taking the study medication was higher with combination therapy than with captopril alone ($P=0.007$).
 - Therapy was discontinued more frequently for hypotension or renal disease with combination therapy than with captopril ($P\leq 0.05$).

Valsartan compared with enalapril (monotherapy) (n=1)

- In the HEAVEN (Heart Failure Exercise Capacity Evaluation) trial, in patients with stable, symptomatic heart failure on an ACE-I, valsartan was not inferior to enalapril as assessed with the 6-minute walk test at 12-weeks follow-up.
- Quality of life and symptom assessment were similar between groups.
- The rate of overall adverse events was also similar between groups.

Detailed assessment

A total of 14 randomized controlled trials (in 27 publications)^{13, 14, 26-37} compared ACE-Is to AIIRAs among patients with heart disease, including heart failure, left ventricular dysfunction, or coronary heart disease (Table 4, in-text, and Evidence Table 1). The comparisons examined are presented in Table 3. Most studies were of monotherapy of ACE-I compared with AIIRA, however several studies also included a combination ACE-I/AIIRA treatment arm.^{13, 30, 31, 33} In 2 studies the ACE-I or AIIRA were both combined with a diuretic.^{28, 37} The majority of studies were of fair quality, while 3 were rated good quality,^{13, 27, 31} 1 fair-poor³² and 2 poor quality.^{29, 35} Sample size varied widely. Several studies included less than 100 subjects,^{28-30, 35, 37} while the OPTIMAAL trial²⁷ included more than 5 000 subjects, VALIANT¹³ approximately 15 000, and ONTARGET³¹ more than 25 000. A single trial compared aliskiren to placebo in patients with heart failure and hypertension.³⁸

Table 3. Randomized controlled trials comparing ACE-I and AIIRA in populations with heart disease

	Captopril	Enalapril	Ramipril
Candesartan		RESOLVD (McKelvie 1999, ³³ HF ^a)	
Irbesartan			Yip 2008, ³⁷ HF
Losartan	ELITE (Pitt 1997), ³⁴ HF ELITE II (Pitt 2000, ¹⁴ HF OPTIMAAL (Dickstein 2002), ²⁷ MI with HF or ↓ EF	Dickstein 1995, ²⁶ HF Guazzi 1999, ³⁰ HF ^a Guazzi 1997, ²⁹ HF ^b Lang 1997, ³² HF Vescovo 1998, ³⁵ HF ^b	
Telmisartan		REPLACE (Dunselman 2001), ²⁸ HF	ONTARGET 2008, ³¹ CVD ^a
Valsartan	VALIANT (Pfeffer 2003), ¹³ MI with HF or LVSD ^a	Willenheimer 2002, ³⁶ HF	

Abbreviations: CVD, cardiovascular disease; EF, ejection fraction; HF, heart failure; LVSD, left ventricular systolic dysfunction MI, myocardial infarction.

^a Studies with a combination arm also.

^b Poor-quality studies

No studies were identified in populations with heart disease that examined benazepril, cilazapril (available only in Canada), fosinopril, lisinopril, moexipril (not available in Canada), quinapril, perindopril, trandolapril, eprosartan, or olmesartan (not available in Canada).

Aliskiren compared with placebo (combination therapy) (n=1)

In a fair-quality trial (N=302) of patients with heart failure and hypertension on an ACE-I or an ARB, there were no significant difference in serum creatinine between aliskiren and placebo after 3 months of therapy.³⁸ Rates of overall discontinuation of the study drug were similar between groups: 7.5% in the placebo group and 9.0% with aliskiren. There were no significant differences between aliskiren and placebo in rates of withdrawal due to adverse events or for rates of any individual adverse event. Results of subgroup analyses based on demographics, comorbidities, or concomitant medication use were not reported.

Candesartan compared with enalapril (monotherapy and combination therapy) (n=1)

In the RESOLVD trial (Randomized Evaluation of Strategies for LV Dysfunction, Pilot Study), an international, multicenter, placebo-controlled, out-patient trial of fair quality, McElvie and colleagues^{33, 39} compared enalapril 10 mg twice daily plus placebo, enalapril 10 mg twice daily plus candesartan (randomized to 4, 8, or 16 mg daily), and candesartan alone (4, 8, or 16 mg daily). Subjects had heart failure (New York Heart Association classification II, III, or IV) with an ejection fraction < 40%. At 43-week follow-up, there were no statistically significant (defined as $P < 0.05$) differences between treatment groups in the 6-minute walk test, New York Heart Association classification, rates of death, heart failure or other hospitalizations, quality of life, renal dysfunction, or symptomatic hypotension.

RESOLVD was stopped 6 weeks early due to concern by an external monitoring committee that mortality and heart failure hospitalization rates were higher with candesartan. Death rates at week 43 were 3.7% for enalapril, 6.1% for candesartan, and 8.7% for combination therapy (between-group $P = 0.15$). Because this was a pilot study, there were no predetermined stopping rules and the study was not powered for mortality.

Irbesartan compared with ramipril (monotherapy combined with diuretic) (n=1)

In a small, fair-quality trial (N=150), Yip and colleagues³⁷ randomized subjects with heart failure in Hong Kong on stable doses of diuretics to: 1) continued diuretic usage; 2) irbesartan up to 75 mg daily plus diuretic; or 3) ramipril up to 10 mg daily plus diuretic. At 52-week follow-up, the 6-minute walk test did not change significantly in any treatment group ($P > 0.05$) and there was no significant difference among groups. A total of 2 deaths occurred: 1 each in the irbesartan and diuretic groups. Quality of life improved in all 3 treatment groups ($P < 0.01$), with no significant difference between groups. Hospitalization rates for heart failure were similar between groups (P value not reported).

Losartan compared with captopril (monotherapy) (n=3)

Three large, multicenter, international, double-blind, fair-quality, randomized controlled trials compared losartan with captopril.^{14, 27, 34} Two of these trials examined heart failure populations,^{14, 34} while the third examined a population with acute myocardial infarction combined with heart failure or a new Q-wave anterior wall myocardial infarction.²⁷ All 3 trials were of monotherapy of losartan compared with captopril, with either no prior use³⁴ or no recent use of an ACE-I.^{14, 27} Two of the studies were of fair quality;^{14, 34} the third was rated as good quality.²⁷ Evidence for most effectiveness outcomes was graded as moderate (all-cause mortality, cardiovascular deaths, sudden death, cardiovascular disease events, and hospital admissions). New York Heart Association functional class and quality of life were graded as high quality evidence, primarily because results were consistent across studies (Evidence Table 3).

In the first of these trials (ELITE, the Evaluation of Losartan in the Elderly) (N=722),³⁴ persons 65 years of age and older with symptomatic heart failure and left ventricular ejection fraction $\leq 40\%$ with no history of prior use of ACE-I therapy were randomized to either captopril or losartan monotherapy. For the primary composite endpoint of renal dysfunction (an increase in serum creatinine by ≥ 0.3 mg/dL from baseline, confirmed with second test 5-14 days later), at 48 weeks of follow-up the risk reduction with losartan was 2% (95% CI, -51 to 36; $P = 0.63$).³⁴ Death and/or heart failure admissions were decreased with losartan but did not reach statistical significance (risk reduction 32%, 95% CI, -4 to +55; $P = 0.075$). This reduction with losartan was

primarily due to a decrease in all-cause mortality with losartan ($P=0.035$) and the lower total mortality was primarily due to a decrease in sudden cardiac deaths.³⁴ New York Heart Association functional class improved with both losartan and captopril ($P\leq 0.001$ compared with baseline for both groups), with no significant difference between groups.³⁴ Hospital admissions for any reason were lower with losartan than captopril ($P=0.014$), however rates of admissions for heart failure were similar between groups ($P=0.89$).³⁴ Quality of life as measured with the Sickness Impact Profile and the Minnesota Living with Heart Failure Questionnaire improved in both treatment groups, with no significant difference between groups.⁴⁰

As ELITE was not powered for the outcome of survival benefit, Pitt and colleagues explored the unexpected finding of survival benefit in elderly heart failure patients in ELITE³⁴ with a second study, ELITE II.¹⁴ In this latter study, the goal was to examine the potential superiority of losartan over captopril for survival and tolerability. Inclusion criteria in ELITE II were similar to those of ELITE. The study population ($N=3152$) also had symptomatic heart failure, but follow-up was somewhat longer (median 1.5 years). For the primary endpoint of all-cause mortality, deaths with losartan (15.9%) and captopril (17.7%) were similar (hazard ratio, 1.13; 95% CI, 0.95 to 1.35; $P=0.16$).¹⁴ The secondary endpoint, a composite of sudden death or resuscitated arrest, also did not differ significantly between treatment groups (captopril 7.3%, losartan 9.0%; hazard ratio, 1.25; 95% CI, 0.98 to 1.60; $P=0.08$), nor were there significant differences in hospital admissions or admissions for heart failure.¹⁴ Health-related quality of life (measured with the Euroqual-5D) did not change significantly from baseline in either treatment group due to the large effect of nonsurvivors on this outcome (who had a score of 0 at the time of death). Among survivors, however, quality of life improved significantly overall for both groups ($P<0.05$), with no significant difference between groups.

The third trial, OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan),²⁷ was also a large ($N=5477$), multi-center, international, double-blind randomized controlled trial, which aimed to examine both the noninferiority of losartan to captopril as well as the superiority of losartan. The study was rated good quality. The inclusion criteria were somewhat different from ELITE II: patients 50 years of age and older with an acute myocardial infarction, with either heart failure, decreased ejection fraction, evidence of acute or old Q-wave, or anterior myocardial infarction. For the primary outcome of all-cause mortality, there was no statistically significant difference between losartan (18%) and captopril (16%) (relative risk, 1.13; 95% CI, 0.99 to 1.28; $P=0.07$) and this result did not satisfy the pre-specified non-inferiority criterion for losartan.

In OPTIMAAL²⁷ there were no significant differences between treatment groups for prespecified secondary endpoints including sudden death, fatal or non-fatal reinfarction, all-cause hospital admission, and New York Heart Association functional class. The only exception was cardiovascular death, which was more common with losartan (15.3%) than with captopril (13.3%) (relative risk, 1.17; 95% CI, 1.01 to 1.34; $P=0.032$).

In ELITE,³⁴ total withdrawals ($P\leq 0.001$), withdrawals due to adverse events, ($P\leq 0.002$), and withdrawals specifically due to cough (captopril 3.8%, losartan 0%; $P\leq 0.002$), were significantly lower with losartan than captopril. In ELITE II¹⁴ total withdrawals (P value not reported) and withdrawals due to adverse events ($P<0.0001$) and cough ($P<0.001$) were also significantly greater with captopril. In the OPTIMAAL,²⁷ discontinuation of study drug for any reason was much higher with captopril (23%) than with losartan (17%) (relative risk, 0.77; 95% CI, 0.62 to 0.79; $P<0.0001$). Discontinuation due to adverse events was also less with losartan ($P<0.001$).

Harms

In ELITE,³⁴ persisting increase in serum potassium and hypotension were not significantly different between treatment groups ($P>0.05$) and death rates (reported only for the per protocol population) were lower with losartan (3.7%) than with captopril (8.5%; between-group $P=0.013$).³⁴ In ELITE II¹⁴ rates of worsening heart failure were similar between groups (25% both groups). Other adverse events were not reported for this trial.

In the OPTIMAAL trial,²⁷ angioedema was less common with losartan (0.4%) than with captopril (0.8%; $P<0.0001$), as also was cough (losartan, 9.3%; captopril, 18.7%; $P<0.0001$). Hypotension and congestive heart failure were not significantly different between groups.

Subgroup analyses

In ELITE³⁴ the decrease in mortality with losartan was generally consistent across different subgroups, including age, ejection fraction, and New York Heart Association functional class. The exception was a similar mortality in women (9/118 with losartan compared with 8/122 with captopril; P value not reported).³⁴

In ELITE II¹⁴ there was no significant difference between captopril and losartan for all-cause mortality and/or all-cause hospitalization or all-cause mortality and/or all-cause hospitalization due to heart failure for subgroups based on baseline New York Heart Association functional class, ejection fraction, sex, age, history of ischemia, atrial fibrillation, and prior myocardial infarction. Among patients on prior beta-blocker therapy, however, more events occurred with losartan than with captopril for the composite outcomes of all-cause mortality and hospital admissions ($P=0.024$) and for heart failure-related mortality and admissions ($P=0.015$). There was no interaction between treatment and beta-blocker subgroups for the primary outcome of all-cause mortality ($P>0.05$). Event rates were higher for both losartan and captopril in patients not on beta-blockers.

For the primary endpoint of all-cause mortality in OPTIMAAL,²⁷ there was no significant difference between treatment groups for subgroups based on age, sex, diabetes, Kilip class, infarct location, prior myocardial infarction, heart failure, and thrombolytic or beta-blocker use.

Losartan compared with enalapril (monotherapy and combination therapy) (n=5)

Five small trials compared losartan with enalapril, all in populations with stable heart failure.^{26, 29, 30, 32, 35} Four of these studies had short-term follow-up (8 to 12 weeks),^{26, 29, 30, 32} while the fifth had a follow-up period of 6 months.³⁵ Several of these studies involved patients stabilized on an ACE-I,^{26, 32} while others included only subjects with no recent use of ACE-Is or AIIRAs.^{29, 30, 35} Two of the trials were small cross-over studies.^{29, 30} The largest of the 5 trials included only 166 patients.²⁶ The 3 parallel-group studies were all of monotherapy,^{26, 32, 35} while 1 cross-over study³⁰ (N=20) included a placebo, monotherapy with either losartan or enalapril, and a combination group. The other cross-over study included a placebo arm, both drugs as monotherapy, and both monotherapies combined with aspirin.²⁹ Three of these studies were of fair quality^{26, 30, 32} and 2 were of poor quality.^{29, 35} The quality of the body of evidence for the outcomes of quality of life and exercise capacity were assessed as low due to concerns regarding risk of bias and small sample sizes. Other outcomes were not assessed for quality as no more than 1 study examined other relevant outcomes. Poor-quality studies will not be discussed herein.

Exercise capacity improved with both losartan and enalapril, with no significant difference between monotherapy treatment groups.^{26, 29, 32} Symptoms also improved in 1 study,

with no significant difference between monotherapy groups, although the incidence of pulmonary rales increased more with losartan 50 mg than with enalapril 20 mg daily ($P<0.05$).²⁶ In the second study reporting on symptoms, Lang and colleagues³² noted that the majority of patients did not improve with respect to symptoms or signs of heart failure, with no significant difference between lisinopril 25 mg, lisinopril 50 mg, and enalapril 20 mg daily. In that same study, the dyspnea-fatigue index improved with lisinopril 25 mg only ($P=0.03$).

The only data available on combination therapy compared with monotherapy³⁰ indicated that quality of life as measured with the Minnesota Living with Heart Failure questionnaire improved slightly with enalapril and lisinopril monotherapy compared with placebo ($P>0.05$), with no further improvement with the 2 drugs in combination.

These trials provided few data on adverse events. Minor increases in serum creatinine, blood urea nitrogen,²⁶ and potassium³² were reported with enalapril compared with losartan, but were not considered clinically significant. Cough was only reported in 1 study, with no significant differences between enalapril and losartan 25 and 50 mg daily.²⁶

Subgroups

There were no significant interactions between treatment and subgroups based on age, sex, and New York Heart Association functional class in 2 studies examining subpopulations.^{26, 32}

Telmisartan compared with enalapril (monotherapy plus diuretic) (n=1)

The REPLACE (the replacement of angiotensin converting enzyme inhibition) trial²⁸ involved patients with stable heart failure on a diuretic and enalapril 10 mg twice daily who were then randomized to continuation of enalapril 10 mg twice daily or to various telmisartan dosages (10, 20, 40, 60 mg daily). There was no significant difference within any treatment group at 12 weeks of follow-up, nor were there any significant differences between any telmisartan group and enalapril for exercise duration, New York Heart Association classification, or quality of life. One or 2 deaths occurred in each treatment group. Rates of 1 or more adverse events were reported as similar across treatment groups (overall rate of 54%), but group-specific rates were not reported. Cough was more common with enalapril, but not significantly different from rates with telmisartan ($P=0.30$). No data on subgroups were reported.

Telmisartan compared with ramipril (monotherapy and combination therapy) (n=1)

A large, double-blind, non-inferiority, randomized, good-quality trial (N=25 620) compared ramipril 10 mg daily, telmisartan 80 mg daily, and combination therapy in patients with vascular disease or diabetes with end-organ damage but without symptomatic heart failure (ONTARGET, The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial).³¹ At a median follow-up of 56 months, telmisartan was not inferior to ramipril for the prespecified primary outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure (relative risk, 1.01; 95% CI, 0.94 to 1.09; $P=0.004$ compared with predefined noninferiority boundary). Results were also consistent across all components of this outcome. In addition, telmisartan was not inferior to ramipril for the secondary composite outcome of death from cardiovascular causes, myocardial infarction, or stroke (the primary outcome of the HOPE trial) (relative risk, 0.99; 95% CI, 0.91 to 1.07; $P=0.001$ for noninferiority). There were no significant differences between ramipril and telmisartan in deaths, revascularization, hospitalization or worsening or new angina, new diagnosis of diabetes, or heart failure.

In ONTARGET, combination therapy with telmisartan and ramipril was not significantly better than ramipril alone for the primary outcome (relative risk, 0.99; 95% CI, 0.92 to 1.07), with nonsignificant differences also for the secondary outcomes noted above.

For the secondary outcome of renal impairment (no specific definition was used, rather the definition was based on report of an event that led to discontinuation of the drug), ramipril and telmisartan had a similar relative risk (1.09; 95% CI, 0.74 to 1.61).³¹ The relative risk of renal impairment with combination therapy was, however, significantly increased (1.37; 95% CI, 1.22 to 1.44; $P<0.001$).³¹ Rates of renal dialysis were not significantly different across the 3 treatment groups. For the primary renal composite outcome of dialysis, doubling of serum creatinine, and death, event rates were similar for telmisartan and ramipril, but were increased with combination therapy (hazard ratio, 1.09; 95% CI, 1.01 to 1.18; $P=0.037$).⁴¹ The secondary renal outcomes of dialysis or doubling of creatinine were also similar with the 2 monotherapies, but increased with combination therapy (hazard ratio, 1.24; 95% CI, 1.01 to 1.51). On the other hand, the increase in urinary albumin excretion was less with telmisartan ($P=0.004$) or combination therapy ($P=0.001$) than with ramipril.⁴¹

Harms

More subjects permanently discontinued ramipril as monotherapy or combination therapy because of cough or angioedema than telmisartan monotherapy. More subjects stopped telmisartan due to hypotension symptoms than ramipril. Discontinuation due to hypotension, syncope, diarrhea, or renal impairment was more likely to occur with combination therapy than with ramipril monotherapy ($P<0.05$).³¹

Subpopulations

For the primary composite outcome, results were similar between ramipril and telmisartan and between ramipril and combination therapy for subgroups based on cardiovascular disease, systolic blood pressure, diabetes, age, or sex.³¹

Valsartan compared with captopril (monotherapy and combination therapy) (n=1)

VALIANT (Valsartan in Acute Myocardial Infarction Trial)^{13, 42-47} was a large (N=14 703), international, multi-center trial of patients with an acute myocardial infarction 0.5 to 10 days prior to enrollment, complicated by heart failure and/or evidence of left ventricular systolic dysfunction. Subjects were randomized to 1 of 3 treatment groups, with the goal of titrating up to the following dosages at the 3-month post-hospitalization visit as indicated by the patient's clinical status: 160 mg valsartan twice daily; valsartan 80 mg twice daily plus 50 mg captopril 3 times daily; or captopril 50 mg 3 times daily. During median follow-up of 24.7 months, there was no statistically significant difference in death rates between the valsartan and captopril groups ($P=0.98$), or between the combination therapy group and the captopril group ($P=0.73$). Valsartan was not inferior to captopril for mortality ($P=0.004$) and for the composite endpoint of fatal and nonfatal cardiovascular events ($P<0.001$). Quality of life and annual rates of hospitalization were not significantly different among the treatment groups ($P>0.05$ for valsartan and combination therapy compared with captopril). The percentage of patients not taking the study medication at the end of the study was higher with combination therapy than with captopril alone ($P=0.007$).

Harms

Hypotension and renal disease were more common reasons for therapy discontinuation with combination therapy than with captopril ($P<0.05$), while cough was a more common reason with captopril monotherapy ($P<0.05$).

Subpopulations

In the main trial,¹³ subgroups based on age, sex, diabetes, prior myocardial infarction, heart failure, left ventricular dysfunction, or prior ACE-I use did not produce significant differences in the effects of treatment on risk of death or on the secondary composite cardiovascular endpoint for either valsartan or combination therapy compared with captopril ($P>0.05$).

Prisant and colleagues⁴⁵ performed a subset analysis on VALIANT, including 3790 white and 340 African-American patients. These researchers noted that effects across the 3 treatment groups were similar for African-Americans for primary and secondary outcomes. African-Americans were more likely than white subjects to develop renal dysfunction and hyperkalemia requiring valsartan discontinuation, but this difference was not significant after adjusting for baseline renal insufficiency ($P=0.13$). Angioedema was rare, but among patients treated with captopril, African Americans were almost twice as likely to develop angioedema as whites, although the result was not statistically significant (2.1% compared with 1.2%, $P=0.2$).

Valsartan compared with enalapril (monotherapy)

The HEAVEN trial (Heart Failure Exercise Capacity Evaluation),³⁶ rated fair quality, examined the noninferiority of valsartan compared with enalapril in patients with stable, symptomatic heart failure on an ACE-I. Subjects were randomized to valsartan (up to 160 mg daily) or enalapril (up to 10 mg twice daily). The change in the 6-minute walk test distance at 12-week follow-up suggested that valsartan was not inferior to enalapril (least squares mean treatment difference (valsartan minus enalapril) was 1.12 meters (95% CI, -21.89 to +24.12 meters; $P<0.001$ for noninferiority, $P=0.462$ for superiority of valsartan)). There was no significant difference between groups in the dyspnea-fatigue index and in quality of life as measured with the Minnesota Living with Heart Failure Questionnaire. There was no significant difference between treatment groups for overall rate of adverse events, although serious adverse events were more common with enalapril (no statistics reported).

Subpopulations

Age (<65 years compared with ≥ 65 years), sex, pre-randomization beta-blocker use, New York Heart Association class, and etiology of heart failure did not differ between the 2 treatment groups with regard to the outcomes of quality of life and dyspnea-fatigue index.

Table 4. AIIRA drugs compared with ACE-I drugs in populations with heart failure or cardiovascular disease

Study, year Country Trial name Quality	Study design Follow-up interval Population	Intervention	Results	Withdrawals and adverse events
Candesartan compared with enalapril				
McKelvie RS 1999 ³³ Tsuyuki RT, 1997 ³⁹ Canada, Switzerland, US, Italy RESOLVD: Randomized Evaluation of Strategies for LV Dysfunction, Pilot Study	RCT Follow-up: 43 weeks Heart failure	Stage 1: E: Enalapril 10 mg bid + placebo (n=109) E+C: Enalapril 10 mg bid + candesartan 4 or 8 mg qd (n=332) C: Candesartan: randomized to 4, 8, or 16 mg qd (n=327)	CHF hospitalization ($P=0.09$), any hospitalization, renal dysfunction: NSD among groups Deaths at up to 43w: C 16 mg 4.6%, C 16 mg + E 11.4%; E 20 mg 3.7% ($P=0.15$) 6-min walk test at 43w: NSD among groups NYHA classification: NSD among 3 groups at 18 or 43w Quality of life: NSD between groups	Withdrawals: NR Symptomatic hypotension: NSD between groups: C 16 mg 0.9%; C+E: 1.8%; E 20 mg 0.93%
Fair				
Irbesartan compared with ramipril				
Yip GWK 2008 ³⁷ Hong Kong Fair	RCT Follow-up 52 weeks Heart failure	D: Diuretic: either furosemide or thiazide (n=50) I: Irbesartan 18.75 mg qd titrated to 75 mg qd + diuretic (n=56) R: Ramipril 2.5 titrated to 10 mg qd + diuretic (n=45)	6-min walk test: increased slightly in all groups; NSD within or between groups (between-group $P=0.8$) Cardiovascular deaths (number): diuretic 1, irbesartan 1, ramipril 0 Quality of life measured with Minnesota Heart Failure Symptom Questionnaire: improved all 3 groups by 12w ($P<0.01$); NSD between groups (P value NR) Readmission for HF: diuretic 12.2%, irbesartan 11.1%, ramipril 11.4% (P values NR)	Withdrawals: 12 total AEs: NR

Study, year Country Trial name Quality	Study design Follow-up interval Population	Intervention	Results	Withdrawals and adverse events
Losartan compared with captopril				
Dickstein K 2002 ²⁷	RCT, parallel group	L: Losartan 12.5 mg qd, titrated to 50 mg qd (n=2744)	All-cause mortality (%): L 18%, C 16%, RR, 1.13 (95% CI, 0.99 to 1.28), <i>P</i> =0.07; did not satisfy the non- inferiority criterion	Discontinuation of study drug for any reason: L 17%, C 23%, RR, 0.77 (95% CI, 0.62 to 0.79), <i>P</i> <0.0001 Discontinuation due to AEs: L 7%, C 14%, RR, 0.50 (95% CI, 0.42 to 0.59), <i>P</i> <0.001
Norway, USA, UK, Germany, Sweden, Ireland, Denmark	Mean follow-up 2.7 (0.9) years	C: Captopril 12.5 mg tid, titrated to 50 mg tid (n=2733)	Sudden death: RR, 1.19 (95% CI, 0.99 to 1.43), <i>P</i> =0.072	Angioedema: L 0.4%, C 0.8%, <i>P</i> =0.034 Hypotension: L 13.3%, C 16.3%, <i>P</i> =0.002 CHF: L 14.6%, C 14.0%, <i>P</i> =0.537 Angioedema: L 0.1%, C 0.5%, <i>P</i> =0.019
OPTIMAAL: Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan	Acute MI and HF or decreased EF or other evidence CHD		Fatal or nonfatal reinfarction: RR, 1.03 (95% CI, 0.89 to 1.18), <i>P</i> =0.72 Cardiovascular deaths: RR, 1.17 (95% CI, 1.10 to 1.34), <i>P</i> =0.032	
Good			All-cause hospital admission: RR, 1.03 (95% CI, 0.97 to 1.10), <i>P</i> =0.36	
Pitt B, 1997 ³⁴ Cowley AJ, 2000 ⁴⁰ Konstam MA 2000 ⁴⁸ (ventricular function substudy) Pitt B 1995 ⁴⁹ (rationale and design) Houghton AR 1999 ⁵⁰ (exercise effects substudy)	RCT Follow-up 48 weeks Heart failure	C: Captopril: 6.25 mg titrated to 12.5, 25, 50 mg tid + losartan placebo; mean dosage achieved 122.7 mg qd (n=370) L: Losartan: 12.5 mg titrated to 25, 50, qd + captopril placebo; mean dosage achieved 42.6 mg qd (n=352)	Renal dysfunction (primary composite endpoint): C: 10.5%, L: 10.5%; risk reduction 2% (95% CI, -51 to 36%), <i>P</i> =0.63 Death and/or HF admissions: C: 13.2%, L: 9.4%; risk reduction 32% (95% CI, -4 to 55), <i>P</i> =0.075 NSD within or between groups in 100-m corridor walk test or in pedometer scores (Houghton 1999) Hospital admissions (Pitt 1997) Total: C 29.7%, L 22.2%, <i>P</i> =0.014 For HF: C 5.7%, L 5.7%, <i>P</i> =0.89	Total withdrawals (including deaths): C: 30.0%, L: 18.5%, <i>P</i> <0.0001 Withdrawals due to AEs (excluding death): C: 20.8%, L: 12.2%, <i>P</i> ≤0.002 Deaths (per protocol): L: 3.7%, C: 8.5%, <i>P</i> =0.013 Persisting increase in potassium of ≥ 0.5 mml/L C; 22.7%, L 18.8%, <i>P</i> =0.069 Hypotension-related symptoms: 24% overall, <i>P</i> >0.05 Worsening HF: C 9/370; L 3/352 (<i>P</i> value NR)
289 centers in 46 countries				
ELITE (Evaluation of Losartan in the Elderly)				
Fair				

Study, year Country Trial name Quality	Study design Follow-up interval Population	Intervention	Results	Withdrawals and adverse events
Pitt B, 2000 ¹⁴ Konstam MA, 2005 ⁵¹ Pitt B 1999 ⁵² (rationale, design, baseline characteristics)	RCT Follow-up: median for each group: 1.5 years	C: Captopril: 6.25 mg titrated to 12.5, 25, 50 mg tid + losartan placebo (n=1574) L: Losartan: 12.5 mg titrated to 25, 50, qd + captopril placebo (n=1578)	All-cause mortality (%): L 17.7; C 15.9; hazard ratio, 1.13 (95% CI, 0.95 to 1.35) <i>P</i> =0.16 Sudden death or resuscitated arrest, %: C 7.3, L 9.0, hazard ratio, 1.25 (95% CI, 0.98 to 1.60), <i>P</i> =0.08 NSD hospital admissions or admissions for heart failure Health-related quality of life: no significant change in either group overall; among survivors both groups improved with NSD between groups	Total withdrawals (excluding deaths): C 14.0%, L 7.9% (<i>P</i> value NR) Withdrawals due to AEs: C 20.8%, L 12.2%, <i>P</i> <0.001 Worsening HF: C 25%, L 25%
US, UK, Norway, Germany ELITE II (Evaluation of Losartan in the Elderly)	Heart failure			
Fair				
Losartan compared with enalapril				
Dickstein K 1995 ²⁶	RCT Follow-up: 8 weeks	L25: Losartan 25 mg qd (n=52) L50: Losartan 50 mg qd (n=56) E: Enalapril 20 mg qd (n=58)	Exercise capacity (6-min walk test) at 8w: <i>P</i> >0.05 within and between groups Dyspnea-fatigue Index profile (8w): improved with losartan 25 mg (<i>P</i> <0.05) and enalapril (<i>P</i> <0.001); NSD between groups Incidence of worsening symptoms (exertional dyspnea, edema, orthopnea, worsening NYHA class): NSD among treatment groups; functional class improved in 30% overall, evenly distributed across groups Pulmonary rates, increased in all groups, L50 > E, <i>P</i> <0.05	Withdrawal due to AEs (number patients): losartan25: 1, losartan50: 2, enalapril5: (NSD among groups) Blood urea nitrogen, creatinine, potassium: increased with enalapril, decrease in losartan (both groups), <i>P</i> <0.05; none considered clinically significant
Norway, Sweden, Finland Fair	Heart failure			
Guazzi M 1997 ²⁹	RCT, cross- over, 3 weeks of treatment for each treatment	Total n=16 + 8 healthy controls Randomized to receive the following sequence, or in reverse order (3w each):	Exercise tolerance: NSD between any 2 groups	NR
Italy Poor	Each treatment for 8 weeks Heart failure	P: Placebo E: Enalapril 10 mg		

Study, year Country Trial name Quality	Study design Follow-up interval Population	Intervention	Results	Withdrawals and adverse events
		bid L: Losartan 50 mg qd E+A: Enalapril + ASA 325 mg qd L+A: Losartan + ASA		
Guazzi M 1999 ³⁰ Italy Fair	RCT, cross- over (at 8- week intervals) Each treatment for 8 weeks Heart failure	Total n=20 Randomized to receive the following sequence, or in reverse order: P: Placebo+placebo E: Enalapril 20 + placebo L: Losartan 50 mg + placebo E+L: Enalapril + losartan Each treatment lasted 8w	Minnesota Living with Heart Failure questionnaire: slight improvement while on E+P and L+P compared with P ($P>0.05$); no further improvement with E+L; NSD between groups	1 patient withdrew due to hypotension on E=P; 1 withdrew due to cough on E
Lang RM 1997 ³² US Fair-poor	RCT, parallel group Follow-up: 12 weeks Heart failure	L25: Losartan 12.5 to 25 mg qd (n=38) L50: Losartan 12.5 to 50 mg qd (n=40) E: Enalapril 2.5 to 10 mg bid (n=38)	6-min walk test (meters) at 12w: NSD between groups Treadmill test: increase L25 $P=0.028$; L 50 $P=0.006$; E 20 $P=0.03$; NSD between any 2 groups Dyspnea-fatigue index: improved with L25 only ($P=0.03$) HF symptoms, worsening HF, change in NYHA class: NSD between groups	Total withdrawals: NR Withdrawals due to AEs: 1 patient from each of 3 treatment groups Any AE (%): L25 65.8, L50 67.5; E20 60.5% Deaths: L25: 1 (sudden death); L 50 5 (sudden death, worsening HF, V arrhythmia, septicemia, unknown cause); E20: 0 NSD between groups at 12w in blood urea nitrogen, potassium, Na+, uric acid Increase in serum Cr (mg/dL) at 12w: L50 < E 20, $P<0.05$; E 20 follow-up > baseline E20, $P<0.05$

Study, year Country Trial name Quality	Study design Follow-up interval Population	Intervention	Results	Withdrawals and adverse events
Vescovo G 1998 ³⁵	RCT, parallel group	Total n=16 (with an additional 8 healthy controls)	Exercise duration: increase in both groups, $P=0.03$ for both L and E; between-group P value NR	NR
Italy Poor	Follow-up: 6 months Heart failure	L: Losartan: to 50 mg qd E: Enalapril: to 10 mg bid		
Telmisartan compared with enalapril				
Dunselman PHJM 2001 ²⁸	RCT, parallel- group	E: Enalapril 10 mg bid (continued from screening phase) (n=77)	Exercise duration: ↑ in all groups; NSD between baseline and follow-up for any group; NSD between any T group and EI NYHA classification: NSD for any group	Total withdrawals: 11 Withdrawals due to AEs: 3 (all telmisartan)
The Netherlands REPLACE (the replacement of angiotensin converting enzyme inhibition) Fair	Follow-up: 12 weeks Heart failure	T10: Telmisartan 10 mg qd (n=75) T20: Telmisartan 20 mg qd (n=72) T40: Telmisartan 40 mg qd (n=77) T80: Telmisartan 80 mg qd (n=77)	Death: 2 on T20; 1 on T40; 1 on T80; 2 on E20 Quality of life (Minnesota Living with Heart Failure): NSD between or within groups	Any AE: 54% overall; similar across treatment groups
Telmisartan compared with ramipril				
The ONTARGET Investigators 2008 ³¹	RCT, parallel group, noninferiority study of AIIRA compared with ACE; superiority of combination to ramipril	R: to 10 mg qd (n=8576) T: Telmisartan 80mg qd (n=8542) R+T: ramipril + telmisartan (n=8502)	Composite, primary outcome (death from CVD causes, MI, stroke, hospitalization for HF): R 16.5%; T 16.7%; R+T 16.3%; RR, T vs. R 1.01 (95% CI, 0.94 to 1.09); RR, R+T vs. R 0.99 (95% CI, 0.92 to 1.07) T < R	Study drug discontinuation: R 23.7%; T 21.0%; R+T 22.7% (both drugs), 6.7% (1 drug) Cough: T < R ($P<0.0001$) Angioedema: T < R ($P=0.01$) Hypotension: T > R ($P<0.001$); T+R > R ($P<0.001$) Renal dysfunction: T+R > R ($P<0.001$)
40 countries ONTARGET: The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial Good	Follow-up median 56 months CVD or diabetes with end-organ damage			

Study, year Country Trial name Quality	Study design Follow-up interval Population	Intervention	Results	Withdrawals and adverse events
Valsartan compared with captopril				
Pfeffer MA 2003 ¹³ Reed SD 2005 ⁴⁶ Prisant LM 2008 ⁴⁵ Anavekar NS, 2008 ⁴³ Anavekar NS, 2004 ⁴² (NEJM) White HD, 2005 ⁴⁷ Anderson RE, 2008 ⁴⁴	RCT Median follow-up: 24.7 months Post MI with HF or LVSD	All dosages titrated up to goal dosage: V: Valsartan 160 mg bid (n=4909) V+C: Valsartan 80 mg bid + 50 mg captopril tid (n=4885) C: Captopril 50 mg tid (n=4909)	Hazard ratio death (97.5% CI) V vs. C: 1.00 (0.90 to 1.11) V+C vs. C: 0.98 (0.89 to 1.09) Hazard ratio for death from CV cause, or MI, or HF hospitalization: V vs. C: 0.95 (97.5% CI, 0.88 to 1.03) V+C vs. C: 0.97 (97.5% CI, 0.89 to 1.05) V not inferior to C for mortality by prespecified criteria Quality of life: NSD among treatment groups	Total withdrawals (%): V: 29.5, V+C: 23.4, C: 21.6 Withdrawals due to AEs (%): V: 5.8, V+C: 9.0, C: 7.7 AEs resulting in permanent discontinuation of treatment (%): Hypotension: V: 1.4 (vs. C, $P<0.05$), V+C: 1.9 (vs. C, $P=0.05$), C: 0.8 Renal causes: V: 1.1, V+C: 1.3 (vs. C, $P<0.05$), C: 0.8 Hyperkalemia: V: 0.1, V+C: 0.2, C: 0.1 Angioedema: V: 0.2, C+V: 0.2, C: 0.3
International (24 countries) VALIANT Valsartan in Acute Myocardial Infarction trial				
Good				
Valsartan compared with enalapril				
Willenheimer R 2002 ³⁶ Sweden HEAVEN Study (Heart Failure Exercise Capacity Evaluation)	RCT, parallel group, non-inferiority of valsartan to enalapril Follow-up: 12 weeks HF	V: Valsartan: to 160 mg qd (n=70) E: Enalapril: to 10 mg bid (n=71)	Change in 6-min walk test distance (ITT population): least squares means treatment difference (V-E): 1.12 m (95% CI, -21.89 to +24.12). $P<0.001$ for noninferiority; superiority $P=0.462$ NSD between groups in the dyspnea-fatigue index and the Minnesota Living with HF Questionnaire	Total withdrawals: V 9/71; E 14/71 Withdrawals due to AEs: V 2/70; E 3/71 Any AE (%): V 50, E 63 ($P>0.05$) Deaths: V 1.4%, E 7.6% Worsening CHF: V 5.7%, E 1.4% Serious AEs: V 9%, E 16% (not defined, included deaths)
Fair				

Abbreviations: AE, adverse event; bid, twice daily; CHD, coronary heart disease; CVD, cardiovascular disease; EF, ejection fraction; HF, heart failure; ITT, intention to treat; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; NSD, no significant difference; NYHA, New York Heart Association; RCT, randomized controlled trial; tid, 3 times daily; qd, once daily; RR, relative risk.

Hypertension

Summary of findings

Comparison of monotherapies

- Losartan compared with enalapril (3 fair-quality trials, 1 poor quality)
 - Effectiveness/efficacy: Evidence from 2 trials did not consistently demonstrate differential effects on creatinine. Glomerular filtration rate increased significantly for losartan (+12%) but not enalapril (+5%) in 1 trial. One trial each found similar effects on quality of life, creatinine clearance, and overall withdrawals.
 - Harms: Significantly lower incidence of overall adverse events for losartan in 1 trial. Incidence of cough-related adverse events was lower for losartan in 3 trials, but the difference was only significant in the largest trial. There were fewer withdrawals due to adverse events for losartan in 2 trials, but the differences were not significant.
 - Subgroups: Comparisons based on subgroups were not reported.
- Losartan compared with captopril, fosinopril, perindopril, quinapril, and ramipril (1 trial each)
 - Effectiveness/efficacy: Changes in serum creatinine were similarly minimal in all groups. Changes in creatinine clearance were similarly minimal for losartan compared with either fosinopril or ramipril. Reduction in albumin excretion rate for losartan was higher than with ramipril and lower than with fosinopril, but the differences were not significant. Overall withdrawals were nonsignificantly lower for losartan than captopril. No deaths in either losartan or fosinopril group.
 - Harms: Only compared between losartan and captopril in 1 trial. Compared to ACEI comparators, there were nonsignificantly fewer overall adverse events, serious adverse events, cough, and withdrawals due to adverse events with losartan. One participant in each group had hyperkalemia.
 - Subgroups: In the overall study population, reduction in albumin excretion rates was only significant for fosinopril, however in the subgroup of participants with microalbuminuria, reductions were significant for both losartan and fosinopril.
- Candesartan compared with enalapril (2 fair-quality trials, 1 poor quality)
 - Effectiveness/efficacy: No significant differences in quality of life between candesartan and enalapril in the 2 fair-quality trials.
 - Harms: No significant differences between candesartan and enalapril in incidence of overall adverse events (1 trial) and withdrawals due to adverse events (1 trial). Incidence of cough was significantly lower for candesartan in 2 trials. There was significantly less discomfort due to cough with candesartan in 1 trial.
 - Subgroups: Comparisons based on subgroups were not reported.
- Candesartan compared with lisinopril and perindopril (1 fair-quality trial each)
 - Effectiveness/efficacy: Similar reductions in albumin excretion rates for candesartan and either lisinopril or perindopril. Overall withdrawals were nonsignificantly lower for lisinopril compared with candesartan.
 - Harms: Withdrawals due to adverse events were nonsignificantly lower for lisinopril compared with candesartan. Nonsignificant differences between

- candesartan and perindopril in incidence of overall adverse events, gastrointestinal-related adverse events, and withdrawals due to adverse events.
 - Subgroups: Neither trial reported comparisons based on subgroup characteristics.
- Valsartan compared with benazepril (1 fair-quality trial), lisinopril (2 trials: 1 good-quality, 1 fair-quality) and ramipril (1 fair-quality trial)
 - Effectiveness/efficacy: There were significantly fewer atrial fibrillation recurrences with valsartan (16%) compared with ramipril (28%) in adults with mild hypertension and symptomatic atrial fibrillation. No other significant differences between valsartan and any ACE-I comparator were found for mortality, renal outcomes, or overall withdrawals.
 - Harms: Significant differences between valsartan and an ACE-I comparator were only found in the largest of the 4 trials, the PREVAIL trial (N=1213). In PREVAIL, incidence of withdrawal due to adverse events, overall adverse events, and cough were significantly lower with valsartan compared to lisinopril.
 - Subgroups: No trial reported comparisons based on subgroup characteristics.
- Eprosartan compared with enalapril (3 fair-quality trials)
 - Effectiveness/efficacy: Differences in mortality (2 trials), quality of life (2 trials), or overall withdrawal (3 trials) were not significant.
 - Harms: Cough-related adverse events were consistently significantly lower for eprosartan in all 3 trials. Incidence of overall adverse events was significantly lower for eprosartan in a 3-month trial of exclusively elderly adults (N=334), but similar to enalapril in a 6-month trial in younger adults (N=529). Differences in withdrawals due to adverse events (2 trials) and serious adverse events (1 trial) were not significant.
 - Subgroups: Incidence of cough was significantly reduced with losartan in older, younger, and Black subgroups from 1 trial.
- Telmisartan compared with enalapril and ramipril (1 trial each, both fair quality)
 - Effectiveness/efficacy: Significant improvements in quality of life were not found for either telmisartan compared with enalapril in a population of exclusively elderly adults. There were no deaths in either the telmisartan or ramipril treatment groups. Significant differences between telmisartan and either enalapril or ramipril were not found in any incidence of overall withdrawals.
 - Harms: Incidence of cough was significantly lower for telmisartan compared with both ACE-I comparator groups. No significant differences between telmisartan and either ACE-I comparator group in overall adverse events, incidence of withdrawals due to adverse events, and incidence of serious adverse events. No significant difference between telmisartan and enalapril in gastrointestinal-related adverse events or angioneurotic edema.
 - Subgroups: Neither trial reported comparisons based on subgroup characteristics.

Combination therapy with AIIRAs and ACE-Is

- Losartan plus ramipril (1 trial, good quality), valsartan plus benazepril (1 trial, fair quality), valsartan plus lisinopril (1 trial, fair quality)
 - Effectiveness/efficacy: All 3 trials found significantly greater reductions in microalbuminuria levels with AIIRA/ACE-I combination therapy compared with ACE-I monotherapy. Combination therapy with losartan/ramipril and

valsartan/benazepril, but not valsartan/lisinopril, also had significantly greater reductions in microalbuminuria levels than AIIRA monotherapy.

- Harms: None of the trials reported any significant differences between the AIIRA/ACE-I combination therapy groups and the AIIRA or ACE-I monotherapy groups.
- Subgroups: No comparisons reported based on subgroup characteristics.

Detailed assessment

Comparison of monotherapies

We included 23 trials (in 28 publications) that compared monotherapy with an AIIRA to monotherapy with an ACE-I in adults with hypertension.⁵³⁻⁸⁰ All but 7 trials^{59, 67, 71, 75, 79-82} were previously evaluated in a good-quality systematic review completed by the Duke Evidence-based Practice Center in November, 2007.^{21, 22} Complete data abstraction for the 16 trials that were included in the Duke Evidence-based Practice Center review can be found in Appendix E of their Final Report, located at the following link:

<http://www.effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=12%20&DocID=48>. Data abstraction for the remaining 6 trials is found in Evidence Table 4. Quality assessments for all 22 trials are found in Evidence Table 5

Enalapril was the most frequent ACE-I monotherapy comparator and losartan the most frequent AIIRA monotherapy comparator.

Losartan

Losartan compared with enalapril

Three of 4 trials of losartan compared with enalapril were rated fair quality.^{56, 73, 76} The other was rated poor quality and its results will not be discussed in detail here.⁵⁴ In 2 trials, losartan and enalapril dosages were titrated based on achievement of blood pressure control goals. In 1 of those trials, participants were started on 50 mg of losartan or 2.5 mg of enalapril, which were titrated to 100 mg and 10 mg, respectively, to achieve blood pressure control of below 140/90 mm Hg.⁷³ In the other trial, losartan was titrated from 12.5 mg up to 50 mg and enalapril from 5 mg up to 20 mg if diastolic blood pressure remained above 90 mm Hg.⁵⁶ In the third trial, participants were given fixed dosages of either losartan 50 mg or enalapril 20 mg.⁷⁶ Follow-up duration was 3 years in 1 trial⁵⁶ and 3 to 4 months in the other 2 trials. The largest trial randomized 407 participants,⁷⁶ whereas the others were much smaller, with 50 or fewer participants.

Effectiveness/efficacy outcomes. Change in serum creatinine was inconsistent in the 2 trials examining this outcome.^{73, 76} In the trial that compared fixed dosages of losartan 50 mg to enalapril 20 mg over 3 months (N=407), there was a significant increase in serum creatinine from 90.3 to 91.8 (+1.7, $P<0.05$) for enalapril, but not for losartan (88.7 to 88.6).⁷⁶ In the smaller trial (N=29), creatinine did not change significantly for either drug over 4 months.⁷³

Other outcomes reported in 1 trial each included change in glomerular filtration rate,⁵⁶ quality of life,⁵⁷ creatinine clearance,⁷³ and overall withdrawals.⁷⁶ In 1 trial of 50 participants, a significant increase in glomerular filtration rate was found after 3 years for losartan 12.5-50 mg, from 96.5 to 108.6 (+12%, $P<0.005$), but not for enalapril 5-20 mg, from 94.8 to 99.8 (+5%, $P=0.085$).⁵⁶ Otherwise, there were no significant differences found between losartan and enalapril on any other efficacy outcomes.

Harms. Incidence of overall adverse events, cough-related adverse events, and overall withdrawals due to adverse events were generally somewhat greater in the enalapril groups. Incidence of overall adverse events was only reported in 1 trial and was significantly greater after 3 months in the enalapril group (45% compared with 32%, $P<0.01$).⁷⁶ Compared with enalapril, fewer participants in the losartan group experienced bother due to cough (2% compared with 12%),⁵⁶ withdrew due to cough (0 compared with 1 of 14 patients, P value not reported),⁷³ and reported cough (1% compared with 12%, $P<0.01$).⁷⁶ Differences between drugs in incidence of withdrawals due to adverse events were not significant, but were generally lower for losartan (range, 0% to 3%) than for enalapril (range, 8% to 12%).^{56, 76}

Subgroups. No trial of losartan compared with enalapril examined subgroups of interest.

Losartan compared with captopril, fosinopril, perindopril, quinapril, and ramipril

One trial each compared losartan 50 mg to captopril 50mg,⁶⁸ fosinopril 10 mg,⁶³ perindopril 4 mg,⁶⁰ quinapril 10 mg,⁷⁷ and ramipril 5 mg.⁷¹ Sample sizes ranged across trials from 33⁶³ to 396⁶⁸ participants. Trial durations ranged from 3 months^{60, 68} to 1 year.⁷⁷ The trial with the longest duration was rated poor quality because blinding was not used and insufficient information was provided to determine whether baseline characteristics were balanced across treatment groups, whether attrition was high or differential across groups, or how many participants were included in the efficacy analysis.⁷⁷ The other trials were rated fair to good quality.

Participant characteristics varied across trials. The trials that compared losartan to fosinopril and perindopril enrolled participants with hypertension plus type 2 diabetes.^{60, 63} In 1 of those trials, participants with macroalbuminuria were excluded and changes in albumin level (g/l) and urinary albumin excretion rate (mg/day) were evaluated for the whole sample and separately for the 55% of participants who were normo albuminuric and the 45% who had microalbuminuria.⁶³ In the trial that compared losartan to ramipril, albumin levels at baseline or at the end of the trial were not reported.⁶⁰ In a third trial, participants were nondiabetic and had normal renal function, but were macro albuminuric (baseline mean ranged from 350 mg/24 hours to 460 mg/24 hours).⁷¹

Effectiveness/efficacy outcomes. Effect on creatinine was reported in all 4 trials. Changes were minimal and there were no significant differences between losartan and any of the ACE-I comparators. There were no significant differences in change in creatinine clearance (mg/min) between losartan and either fosinopril (-34% compared with -27%)⁶³ or ramipril (-1% compared with +3%).⁷¹ Effects on albumin were reported in 2 trials.^{63, 71} In the trial of 33 participants with type 2 diabetes and either normo albuminuria or microalbuminuria, compared with baseline, reduction in albumin excretion rate (mg/day) over 6 months was statistically significant in the fosinopril group overall (-75%), but was not significant in the losartan group overall (-37%).⁶³ For the subgroup of participants with normo albuminuria (18 of 33), albumin excretion rates increased by 45% for losartan and by 27% for fosinopril.⁶³ In the subgroup of participants with microalbuminuria (15 of 33), albumin excretion rates decreased by 91% in the fosinopril group ($P<0.05$) and by 55% in the losartan group ($P<0.05$). In the trial of 51 participants with nondiabetic macroalbuminuria, the reduction in urinary albumin excretion rate (g/day) was -40% for losartan and -25% for ramipril, but the difference was not statistically significant.⁷¹ Overall withdrawals within individual treatment groups was only reported in 1 trial and were slightly greater for captopril (12%) compared with losartan (8%).⁶⁸

Harms. No significant differences were found between losartan and captopril in the only trial that reported harms within individual treatment groups.⁶⁸ Greater numbers of participants in the captopril group reported any adverse events (41% compared with 33%), serious adverse events (5% compared with 2%), cough (7% compared with 6%), and withdrew due to adverse events (6% compared with 3%). There was only 1 case of hyperkalemia in each treatment group.

Subgroups. The only subgroup analysis reported among these 4 trials was based on baseline albumin levels and results were described above.⁶³

Candesartan

Candesartan compared with enalapril

We included 3 trials that compared starting doses of candesartan 8 mg to enalapril 10 mg.^{66, 69, 75} The trials ranged in duration from 2 months⁷⁵ to 6 months.⁶⁶ Sample sizes ranged from 129 participants⁶⁶ to 429 participants.⁶⁹ In 2 trials, the candesartan and enalapril dosages were doubled after 6 weeks if the diastolic blood pressure was at or above 90 mm Hg⁶⁶ or if the overall blood pressure was at or above 130/85 mm Hg.⁶⁹ In the third trial, there was the possibility to add hydrochlorothiazide 12.5 if diastolic blood pressure was above 105 mm Hg.⁷⁵

The trial with the largest sample size (N=429) was rated poor quality due to the presence of a higher albumin/creatinine ratio at baseline for the candesartan group (112.4 mg/g) compared with the enalapril group (40.4 mg/g) and the exclusion of 26% of participants from the change in albumin/creatinine ratio, and its results will not be discussed here.⁶⁹ The remaining 2 trials were rated fair quality and 63%⁷⁵ and 100%,⁶⁶ respectively, of their participants were female.

Effectiveness/efficacy outcomes. The only eligible outcome reported in both fair-quality trials was quality of life and there were no significant differences between candesartan and enalapril on overall quality of life in either trial.^{66, 75}

Harms. Incidence of overall adverse events was only reported in 1 trial and the rate was 60% for candesartan compared with 67% for enalapril (*P* value not reported).⁶⁶ Incidence of cough was reported in both fair-quality trials. The primary aim of 1 of the trials was to evaluate the effect of candesartan on cough in individuals with confirmed cough during an enalapril challenge period.⁷⁵ After 8 weeks, the proportion of participants with cough had significantly decreased with candesartan (35%) compared with enalapril (68%, *P*<0.001). In the trial of all women (N=129), incidence of cough after 6 months was 0% for candesartan and 13% for enalapril (*P*<0.001) and scores on the Subjective Symptoms Assessment profile revealed more discomfort from dry cough with enalapril than with candesartan (estimated mean difference -0.9; 95% CI, -1.25 to -0.63).⁶⁶ Withdrawals due to adverse events after 2 months were somewhat higher for enalapril (8%) compared with candesartan (4%) in the only trial that reported this outcome, but the difference was not statistically significant.

Subgroups. Neither fair-quality trial reported results on the comparison of candesartan to enalapril based on any subgroup characteristics.

Candesartan compared with lisinopril and perindopril

Candesartan was also compared with lisinopril 10 mg (N=70)⁷² and to perindopril 4 mg (N=96)⁵⁷ in 1 trial each, both of which were rated fair quality, were 12 months in duration, and enrolled hypertensive adults with type 2 diabetes. In the trial involving perindopril, the dosage of candesartan was fixed at 16 mg and participants with any evidence of nephropathy (albumin excretion rates of below 30 mg per 24 hours) were excluded.⁵⁷ In the trial that involved a comparison to lisinopril, the dosage of candesartan was started at 8 mg, but when the target

blood pressure of 130/85 mm Hg was not reached, concomitant treatment with hydrochlorothiazide 12.5 mg was added, followed by a doubling of the candesartan dosage, and additional antihypertensive drugs were added in a step-wise manner.⁷² In this trial, 20% of participants were micro albuminuric and the remainders were normo albuminuric.

Effectiveness/efficacy outcomes. Both trials reported change in albumin excretion rate and there were no significant differences between candesartan and either lisinopril or perindopril. In the trial that compared candesartan to perindopril, reduction in albumin excretion rates –44% and –47%, respectively.⁵⁷ In the trial that compared candesartan to lisinopril, reductions were only displayed in graphical form.⁷² Rate of overall withdrawals was 17% in the candesartan group and 4% in the lisinopril group (*P* value not reported).⁷²

Harms. There were no significant differences between candesartan and either lisinopril or perindopril. Compared with lisinopril (4%), the proportion of participants who withdrew due to adverse events was somewhat greater for candesartan (12%), but the difference was not statistically significant.⁷² There were no significant differences between candesartan and perindopril in proportions of participants with any adverse event (10% compared with 6%), cough (0% compared with 4%), or gastrointestinal-related adverse events (2% in both groups), and no participant withdrew from either group due to adverse events.⁵⁷

Subgroups. Neither trial reported results of the comparison of candesartan to lisinopril or perindopril based on any subgroup characteristics.

Valsartan

Valsartan compared with benazepril, lisinopril, and ramipril

We included 2 trials of valsartan compared with lisinopril^{65, 80} and 1 trial each of valsartan compared with benazepril 10 mg⁷⁹ or ramipril 5 mg to 10 mg.⁵⁹ The “Blood Pressure Reduction and Tolerability of Valsartan in Comparison with Lisinopril” (PREVAIL) trial was rated good quality and compared 4 months of treatment with either valsartan 160 mg or lisinopril 20 mg, both in combination with low-dose hydrochlorothiazide, in 1213 adults with mild to severe hypertension.⁶⁵ In the fair quality VALERIA trial, 133 adults with hypertension and microalbuminuria were randomized to 30 weeks of treatment with either lisinopril 40 mg, valsartan 320 mg, or a combination of valsartan/lisinopril 320/20 mg.⁸⁰ In VALERIA, 73% of participants also had type 2 diabetes. In a fair-quality, 3-month trial of 90 adults with stages 1 or 2 hypertension (European Society of Cardiology), participants were randomized to valsartan 80 mg or benazepril 10 mg.⁷⁹ Dosages of valsartan and benazepril were doubled after the first 2 weeks if the blood pressure remained at or above 140/90 mm Hg, and hydrochlorothiazide 12.5 mg was added after the fourth week if the blood pressure goal was still not met. Valsartan was compared with ramipril in 369 adults with mild hypertension and symptomatic atrial fibrillation in a fair-quality trial with a follow-up duration of 12 months.⁵⁹ Participants were randomized to receive valsartan 160 mg or ramipril 5 mg, and then were titrated after 4 weeks to 240 mg and 7.5 mg, respectively, and after 8 weeks to 320 mg and 10 mg, respectively, to reach a target blood pressure of below 140/90 mm Hg.

Effectiveness/efficacy outcomes. The only significant difference between valsartan and an ACE-I comparator came from the trial of adults with mild hypertension and symptomatic atrial fibrillation, in which the rate of atrial fibrillation recurrence was significantly lower for valsartan (16%; *P*<0.05) compared with ramipril (28%).⁵⁹ Only 1 death occurred across all 4 trials. In the lisinopril group of the VALERIA trial, 1 of 47 participants died (2%).⁸⁰ There were no significant differences in reduction of albumin/creatinine ratio between valsartan and either

benazepril (-35% in both groups)⁷⁹ or lisinopril (-51% compared with -41%).⁸⁰ In the VALERIA trial, microalbuminuria had normalized by the end of the trial for a greater proportion of participants in the valsartan group (31% compared with 17%; *P* value not reported).⁸⁰ There were no significant differences between valsartan and any ACE-I comparator in overall withdrawals in any trial. Overall withdrawal rates were highest in the longest-term trial that compared valsartan to ramipril over 12 months of follow-up (19% compared with 25%).⁵⁹

Harms. Significant differences between valsartan and an ACE-I comparator were only found in the largest of the 4 trials, the PREVAIL trial (N=1213).^{65, 80} In PREVAIL, compared with lisinopril, incidence of withdrawal due to adverse events (1% compared with 4%; *P*=0.01), overall adverse events (5% compared with 11%; *P*=0.001) and cough (1% compared with 7%; *P*<0.001) were significantly lower with valsartan.⁶⁵ In the smaller trials, with sample sizes ranging from 55 to 146 participants, incidence of withdrawal due to adverse events^{59, 79, 80} and cough⁸⁰ were numerically greater, but the differences were not statistically significant.

Subgroups. No trial of valsartan compared with an ACE-I in adults with hypertension reported results of subgroup analyses based on demographics, comorbidities, or concomitant medication use.

Eprosartan

Eprosartan compared with enalapril

We included 3 fair-quality trials (reported in 7 publications) of eprosartan compared with enalapril in adults with hypertension.^{53, 55, 58, 61, 64, 67, 70} Duration of follow-up ranged from 6 weeks⁶⁷ to 6 months.^{53, 55, 58, 61, 64} Sample sizes ranged from 136 participants⁶⁷ to 529 participants.^{53, 55, 58, 61, 64} Two trials involved the comparison of eprosartan 300 mg to enalapril 20 mg.^{53, 55, 58, 61, 64, 67} In the third trial, the starting dose was 600 mg for eprosartan and 5 mg for enalapril.⁷⁰ Eprosartan could be titrated only once, to 800 mg, and enalapril could be titrated first to 10 mg and then to 20 mg, each at 3-week intervals to reach a target systolic blood pressure goal of below 140 mm Hg. Mean age ranged from 56 years to 57 years in 2 trials.^{53, 55, 58, 61, 64, 67} The third trial exclusively enrolled participants aged over 65 years and had a mean age of 73 years.⁷⁰

Effectiveness/efficacy outcomes. Although not powered to be evaluated as a primary outcome, differences in mortality between eprosartan and enalapril were not statistically significant across 2 trials.^{53, 55, 58, 61, 64, 70} In the trial of all elderly participants, there was 1 death in each group (0.6%).⁷⁰ In the second trial, there was 1 death in the eprosartan group (0.4%) and none in the enalapril group.^{53, 55, 58, 61, 64} The death of that participant came 1 month after having an acute myocardial infarction. Changes in quality of life were measured using the Psychological General Wellbeing Index in 2 trials and no significant differences between eprosartan and enalapril were found.^{53, 55, 58, 61, 64, 67} Across the 3 trials, incidence of overall withdrawal ranged from 13% to 15% for eprosartan and 12% to 22% for enalapril, but differences were not statistically significant.

Harms. Results of the comparison between eprosartan and enalapril in incidence of overall adverse events were inconsistent across 2 trials.^{53, 55, 58, 61, 64, 70} After 3 months, in the trial of exclusively elderly participants, more patients in the enalapril group (51%) experienced at least 1 adverse event than those in the eprosartan group (36%; *P* value not reported).⁷⁰ After 6 months in the largest trial of 529 adults with a mean age of 56 years, incidence of adverse events were generally higher than in the shorter-term trial, and the difference between eprosartan (76%) and enalapril (81%) was not statistically significant.^{53, 55, 58, 61, 64} Incidence of withdrawals due to

adverse events was generally low, ranging from 2% to 5% in the eprosartan groups and 9% in the enalapril groups in 2 trials and the differences between drugs were not significant.^{53, 55, 58, 61, 64, 67}

Incidence of serious adverse events was only reported in 1 trial and the difference between eprosartan (1%) and enalapril (3%) was not significant.^{53, 55, 58, 61, 64}

Cough-related adverse events were reported in all 3 trials and incidence was consistently lower for eprosartan compared with enalapril (Table 5). Few participants withdrew due to cough, however, and the difference between eprosartan and enalapril was not significant in 2 trials.^{55, 58, 61, 67}

Table 5. Comparison of eprosartan and enalapril on cough-related adverse events

Author Year	Sample size Duration	Event	Incidence for eprosartan compared with enalapril, P value
Elliott 1999/Breeze 2001/Gavras 1999 ^{55, 58, 61}	N=529 6 months	Gained a definite or possible cough at endpoint	2% vs. 10%, P=0.001
		Coughing as an “on-therapy adverse event”	13% vs. 22%, P=0.004
		Pharyngitis	17% vs. 24%, P=0.03
		Withdrawal due to cough	0.8% vs. 2.3%, P=NS
Rake 2001 ⁶⁷	N=136 6 weeks	All self-reported coughs	5% vs. 23%, P=0.02
		Withdrawal due to cough	2% vs. 4%, P=NS
Ruilope 2001 ^{70a}	N=334 3 months	Cough	1% vs. 6%, P=0.0045

Abbreviations: NS, not significant.

^a Mean age of 73 years.

Subgroups. Results of subgroup analyses of incidence of cough in participants under (N=403) and over (N=125) 65 years of age⁵³ and in those who were black (N=40)⁶⁴ were available from the largest and longest-term trial (6 months) that compared eprosartan to enalapril.^{55, 58, 61} In the total study population, incidence of cough was significantly reduced in the eprosartan group (Table 5), and similar results were found in both the older, younger and Black subgroups of participants.

Telmisartan

Telmisartan compared with enalapril and ramipril

We included 1 trial each of the comparison of telmisartan to enalapril⁶² and ramipril.⁷⁸ Both were rated fair quality. In 801 adults with mild to moderate hypertension (mean ambulatory blood pressure of 148/93 mm Hg, mean age of 54 years, 60% male), open, forced-titration treatment with telmisartan, initiated at 40 mg for 2 weeks and titrated to 80 mg for 12 weeks, was compared with ramipril, initiated at 2.5 mg for 2 weeks and titrated to 5 mg for 6 weeks and then to 10 mg for the last 6 weeks.⁷⁸ In 278 elderly adults with mild to moderate hypertension (mean supine blood pressure of 179/101 mm Hg, mean age of 71 years, 42% male), double-blinded treatment with telmisartan, initiated at 20 and titrated to 40 mg and then 80 mg every 4 weeks as needed, was compared with enalapril, initiated at 5 mg and likewise titrated to 10 mg and then 20 mg.⁶² Study medication was only titrated if the blood pressure remained above 90 mm Hg.

Effectiveness/efficacy outcomes. There were no significant differences between telmisartan and either enalapril or ramipril in effectiveness/efficacy outcomes. In the trial that compared telmisartan and enalapril in elderly adults, significant changes in overall quality of life scores on the SF-36 were not found for either treatment group after 6 months.⁶² In the trial that compared telmisartan to ramipril, there were no deaths in either treatment after 14 weeks.⁷⁸ Incidence of overall withdrawals ranged from 8% to 10% in the telmisartan groups, compared with 11% in each of the enalapril and ramipril groups, respectively, and the differences were not significant.

Harms. The difference between telmisartan and either ACE-I comparator group in incidence of overall adverse events was not statistically significant in either trial. After 14 weeks, incidence of overall withdrawals was 38% for telmisartan and 40% for ramipril.⁷⁸ Compared with the shorter-term trial, incidence of overall adverse events was greater overall after 6 months in elderly adults for both telmisartan (71%) and enalapril (71%).⁶² Differences in incidence of withdrawals due to adverse events were not significant for the comparison of telmisartan (range, 4% to 8%) to either ramipril (5%)⁷⁸ or enalapril (11%).⁶² There was also no significant difference in incidence of serious adverse events for the comparison of telmisartan to enalapril (1.4% compared with 2.9%)⁶² or of telmisartan to ramipril (1% in both groups).⁷⁸ Incidence of cough was significantly lower for telmisartan compared with enalapril (6% and 16%, respectively, $P=0.0139$)⁶² and compared with ramipril (0.5% and 5.7%, respectively, $P<0.001$).⁷⁸ Incidence of gastrointestinal-related adverse events (diarrhea, flatulence, nausea, abdominal pain, constipation, gastritis) and angioneurotic edema (1 person in the enalapril group) were not significantly different between the telmisartan and enalapril groups.⁶²

Subgroups. Neither trial of telmisartan compared with an ACE-I in adults with hypertension reported results of subgroup analyses based on demographics, comorbidities, or concomitant medication use.

Comparison of combination therapy with an AIIRA plus an ACE-I to AIIRA and ACE-I monotherapies in adults with hypertension

We included 6 trials (in 7 publications) that compared combination therapy with an AIIRA plus an ACE-I to AIIRA and ACE-I monotherapy, respectively.^{54, 71, 77, 79-82} Three of these trials were rated poor quality, however, and a detailed analysis of their results will not be provided.^{54, 77, 81, 82} Descriptions of the reasons for their poor quality ratings can be found either above in the ‘monotherapy compared with monotherapy’ section or in Evidence Table 5. Among the remaining 3 trials, 1 was rated good quality⁷¹ and 2 were rated fair quality.^{79, 80} The good-quality trial compared the combination of losartan 50 mg plus ramipril 5 mg to monotherapy with either losartan 50 mg or ramipril 5 mg over 24 weeks in 51 adults who were nondiabetic and had normal renal function, but who were all macro albuminuric (baseline mean albumin excretion rate ranged from 350 mg/24 hours to 460 mg/24 hours).⁷¹ Among the fair-quality trials, 1 compared the combination of valsartan 80 mg plus benazepril 10 mg to monotherapy with either valsartan 80 mg or benazepril 10 mg over 3 months in 90 adults who were nondiabetic with no renal disease, but with microalbuminuria/macroalbuminuria (albumin-to-creatinine ratio).⁷⁹ The other fair-quality trial, the VALERIA trial, compared 30 weeks of treatment with a combination of valsartan/lisinopril 320/20 mg to monotherapy with valsartan 320 mg and lisinopril 40 mg in 133 adults with hypertension and microalbuminuria.⁸⁰ In VALERIA, 73% of participants also had type 2 diabetes.

Effectiveness/efficacy outcomes

All 3 trials found significantly greater reductions in microalbuminuria levels with AIIRA/ACE-I combination therapy compared with ACE-I monotherapy. Reduction in mean albumin-to-creatinine ratio^{79, 80} or albumin excretion rate⁷¹ ranged from 52% to 62% for the AIIRA/ACE-I combination groups, compared with a range of 25% to 41% in the ACE-I monotherapy groups. In 2 of 3 trials,^{71, 79} reduction in microalbuminuria level was also significantly greater for the AIIRA/ACE-I combination therapy compared with the AIIRA monotherapy. However, compared with valsartan monotherapy, reduction in albumin-to-creatinine ratio was not significantly greater with the combination of valsartan/lisinopril (–51% compared with –62%).⁸⁰ None of the trials provided results of formal analyses that ruled out the possibility that the superior reduction in albumin levels in the combination treatment groups could be explained only by differences in blood pressure-lowering effects. But, authors of 1 trial stated that strict blood pressure control protocol used in all treatment groups discounted such a suggestion.⁷¹

No significant changes in creatinine⁷⁹ or creatinine clearance^{71, 79} at the end of treatment were found for any combination treatment or monotherapy groups. There were no significant differences between groups for overall withdrawals in any of the trials.

Harms

The VALERIA trial (N=133), which compared valsartan/lisinopril combination therapy to monotherapy with valsartan and lisinopril, provided the most extensive reporting on harms.⁸⁰ In the VALERIA trial, there were no significant differences between valsartan/lisinopril combination therapy and either valsartan or lisinopril monotherapy groups in overall adverse events (72% compared with 63% or 62%) or withdrawals due to adverse events (8% compared with 7% or 7%). Hypotension was the most frequent adverse event in the valsartan/lisinopril combination therapy group (12%), but the difference as compared to the incidence in the valsartan and the lisinopril monotherapy groups (9% and 2%, respectively) was not statistically significant. There were no withdrawals due to adverse events in the trial that compared losartan/ramipril combination therapy to losartan and ramipril monotherapies.⁷¹ In the trial of valsartan/benazepril combination therapy, the only adverse event-related withdrawals were 2 (7%) participants from the benazepril monotherapy group, both owing to severe cough.⁷⁹

Subgroups

None of the trials involving AIIRA/ACE-I combination therapy in adults with hypertension reported results of subgroup analyses based on demographics, comorbidities, or concomitant medication use.

Nondiabetic Chronic Kidney Disease

Summary of findings

Proteinuric chronic kidney disease: Comparison of monotherapies

- Losartan compared with lisinopril (1 trial; fair quality)
 - Effectiveness/efficacy: A statistically greater reduction in proteinuria was noted for those treated with lisinopril compared with losartan; change in creatinine clearance and blood pressure control were equivalent between groups.

- Harms: Dizziness and hyperkalemia were reported by treatment group and rates were numerically similar between groups.
- Losartan compared with enalapril (3 trials; all fair quality)
 - Effectiveness/efficacy: No statistically significant difference was noted in proteinuria reduction between treatment groups. No statistically significant differences in decline in creatinine clearance were noted.
 - Harms: Harms were not reported by treatment group.
- Losartan compared with benazepril (3 trials; 1 fair quality and 1 good quality)
 - Effectiveness/efficacy: No difference between groups for composite renal survival outcome. No significant difference between groups for reduction in proteinuria. No significant difference in creatinine clearance between groups.
 - Harms: One trial found a statistically significant increase in cough in those treated with benazepril as compared with losartan.
- Losartan compared with trandolapril (1 trial; fair quality)
 - Effectiveness/efficacy: Percent reduction in proteinuria was significant compared to baseline for each group, but no inter-group comparisons were reported. No significant change in creatinine clearance was noted in either group.
 - Harms: Not reported.
- Losartan compared with perindopril (1 trial; fair quality)
 - Effectiveness/efficacy: Numerically greater percent reduction in proteinuria for perindopril group; no analysis available. No significant difference between groups regarding change in creatinine clearance.
 - Harms: Not reported.
- Candesartan compared with lisinopril (1 trial; fair quality)
 - Effectiveness/efficacy: Reduction in proteinuria was numerically similar between groups.
 - Harms: Incidence of hyperkalemia was statistically less likely for those on Candesartan as compared with lisinopril.
- Candesartan compared with trandolapril and perindopril (1 trial; fair quality)
 - Effectiveness/efficacy: Numerically slightly greater percent decline in proteinuria with either ACE-I compared with candesartan at trial completion; no analysis available. There was no statistically significant change in creatinine clearance.
 - Harms: Not reported.
- Valsartan compared with lisinopril (1 trial; fair quality)
 - Effectiveness/efficacy: Changes in proteinuria were not reported in this study. No significant difference between groups for change in glomerular filtration rate.
 - Harms: Not reported.
- Valsartan compared with benazepril (2 trials; both fair quality)
 - Effectiveness/efficacy: No significant difference between groups for reduction in proteinuria. Change in creatinine clearance numerically similar pre and post treatment in 1 trial.
 - Harms: One trial specifically noted no hyperkalemic events in either treatment group. One trial did not report harms.
- Valsartan compared with ramipril (2 trials; both fair quality)
 - Effectiveness/efficacy: Differential effects seen for proteinuria reduction between trials; 1 trial showed no significant difference between groups and 1 showed

significant difference in favor of ramipril but that difference was not independent of blood pressure control. No significant difference between groups for renal function.

- Harms: not delineated by treatment groups.
- Telmisartan compared with enalapril (1 trial; fair quality)
 - Effectiveness/efficacy: No statistically significant difference was noted in percent change in creatinine clearance or mean change in proteinuria between groups.
 - Harms: Numerically more abdominal pain/nausea/gastrointestinal upset events among enalapril compared with telmisartan; otherwise numerically similar adverse events between groups.
- Irbesartan compared with fosinopril (1 trial; fair quality)
 - Effectiveness/efficacy: Percent reduction in proteinuria was numerically similar between groups; no analysis available. Change in renal function was not reported.
 - Harms: There was a numerical difference in rates of occurrence of acute kidney injury and potassium level greater than 5 milli-equivalents per liter for fosinopril compared with irbesartan (2:1 and 2:0 respectively).

Combination therapy with AIIRAs and ACE-Is

Combination of ACE-I and AIIRA compared with monotherapy with either agent

- Combination therapy losartan plus an ACE-I (4 trials)
 - Losartan plus lisinopril (1 trial; fair quality): Differential effect for proteinuria reduction was seen favoring combination therapy, but blood pressure control was not equal between groups. There were no statistically significant changes in creatinine clearance between groups. Rates of hyperkalemia and dizziness were numerically greater in combination therapy arm.
 - Losartan plus enalapril (2 trials; both fair quality): One trial showed greater proteinuria reduction for combination therapy compared with monotherapy but blood pressure was not equivalent between groups. One trial showed equivalent proteinuria reduction between groups at trial completion. Changes in creatinine clearance were not significantly different between groups. Numerically similar rates of dizziness and hyperkalemia for combination therapy and monotherapy with enalapril; numerically slightly fewer events for losartan monotherapy.
 - Losartan plus benazepril (2 trials; both fair quality): Both of these trials found a greater reduction in proteinuria for combination therapy compared with monotherapy. No differential effects between groups for changes in creatinine clearance. Harms were not delineated by treatment groups.
- Combination therapy candesartan plus an ACE-I (1 trial)
 - Candesartan plus lisinopril (1 trial; fair quality): Greater reduction in proteinuria was seen with combination therapy compared with candesartan monotherapy, but not compared with lisinopril monotherapy at time of trial completion. No significant change in creatinine clearance was seen between groups. The incidence of hyperkalemia was statistically less likely in the candesartan group compared with the combination arm.
- Combination therapy with valsartan plus an ACE-I (3 trials)
 - Valsartan plus benazepril (2 trials; both fair quality): One study showed significantly greater reduction in proteinuria with combination compared with

monotherapy, and 1 study demonstrated a significantly greater decline in proteinuria with combination compared with only ACE-I monotherapy. In the latter study blood pressure control was not equivalent between groups. One trial noted increase in glomerular filtration rate for combination therapy greater than for monotherapy, but creatinine clearance changes were not different between treatment groups. One trial noted no hyperkalemic events in either group.

- Valsartan plus ramipril (1 trial; fair quality): No differential effects between groups for proteinuria reduction. Changes in creatinine were similar between groups. Rates of hypotension were similar between groups.
- Combination therapy with irbesartan plus an ACE-I (1 trial)
 - Irbesartan plus fosinopril (1 trial; fair quality): Significantly greater reduction in proteinuria was found for combination compared with monotherapy. No difference was seen in changes in creatinine clearance between groups. Numerically more participants experienced dizziness in combination arm compared with either monotherapy arm; numerically more participants experienced hyperkalemia in combination arm compared with irbesartan arm.

Combination of ACE-I and AIIRA compared with monotherapy with either ACE-I or AIIRA

- Combination therapy of an ACE-I and an AIIRA compared with an ACE-I alone (4 trials)
 - Losartan and lisinopril compared with lisinopril alone (1 trial; fair quality): No differential effects found between groups for proteinuria reduction. Markers for change in renal function were inconsistent; glomerular filtration rate was lower for those on combination therapy but there was no difference between groups in creatinine clearance. Harms were not reported.
 - Combination therapy of candesartan and ramipril compared with ramipril alone (2 trials; both fair quality): Both trials showed a statistically significantly greater decline in proteinuria among IgA (immunoglobulin A) nephropathy patients on combination compared with monotherapy, but that effect was not seen among diabetic nephropathy patients. Creatinine clearance was stable in both groups, both trials. Harms were not delineated by treatment groups or were only delineated for an AIIRA.
 - Combination therapy of irbesartan and ramipril compared with ramipril alone (1 trial; fair quality): No statistically significant difference was found in proteinuria reduction between those groups. Creatinine clearance was stable in both groups. One dizziness/hypotension event occurred with ramipril monotherapy compared with zero with combination therapy; no hyperkalemia events occurred in either group.
- Combination therapy of ACE-I and an AIIRA compared with an AIIRA alone (2 trials)
 - Candesartan and benazepril compared with candesartan alone (1 trial; fair quality): A statistically greater reduction in proteinuria was seen in those on combination therapy compared with monotherapy. Harms were reportedly only for the combination therapy group.
 - Valsartan and benazepril compared with valsartan alone (1 trial; fair quality): A statistically greater reduction in proteinuria was seen only for maximum dose combination therapy compared with monotherapy but blood pressure was not

equivalent between groups. Changes in creatinine were numerically similar between groups. A numerical higher percent rate of hyperkalemia was seen in those on maximum dose combination therapy compared with lower dose combination therapy or monotherapy.

Detailed assessment

Monotherapy: Inter-class comparison of effectiveness, efficacy, and harms between AIIRA and ACE-I

Proteinuric chronic kidney disease

We identified 17 trials⁸³⁻⁹⁵ that compared monotherapy with an angiotensin II receptor antagonist (AIIRA) to monotherapy with an angiotensin converting enzyme inhibitor (ACE-I). 11 were rated as fair quality^{83-87, 89-91, 93-95}, 1 was rated as good quality⁸⁸, and 5 additional identified trials were rated as poor quality.^{92, 96-99} Trials rated as poor will not be discussed in detail, but additional information can be found in Evidence Table 10. Those trials that were rated poorly were heterogeneous in their flaws. Very high withdrawal rate was evident in 2 studies, 1 for a withdrawal rate of 22%,⁹⁹ and 1 with a withdrawal rate of 47%.⁹⁸ The very high withdrawal rate in the latter, coupled with an overall small sample size (N=19, nine of which were withdrawn), was the primary reason for its poor rating. In the former study,⁹⁹ the poor rating stemmed from the lack of statistical analysis of any outcomes of interest and the lack of reporting of any adverse events in addition to the noted small sample size. A third study was rated as poor because the treatment arm groups were different at baseline in terms of both blood pressure and proteinuria, and no adverse events were reported.⁹⁷ The fourth trial that was rated poor quality was the COOPERATE study,⁹⁶ as was one of its sub-studies.⁹² This trial has been a point of much consternation and debate in the medical community; 1 correspondence raised concerns about statistical methods as well as better than expected level of similarity among treatment groups at baseline.¹⁰⁰ Recently, a formal retraction of the COOPERATE study was published by the *The Lancet*.¹⁰¹ Per this retraction statement, a formal investigation of this trial conducted by the original university hospital revealed that this trial was not double blind, that the presence of a statistician during the data analysis was unclear, and that the patient specific data (on a sample chart review) could not be verified to be authentic. For this reason, the COOPERATE trial and its ambulatory blood pressure sub-study were rated as poor and were not included in this report.

Losartan was compared with lisinopril in 1 trial,⁸⁹ to enalapril in 3 trials,^{93, 102, 103} to benazepril in 3 trials,^{88, 94, 104} andtrandolapril in 1 trial,⁹¹ and to perindopril in 1 trial.⁹¹ Candesartan was compared with lisinopril in 1 trial⁹⁰ and to perindopril andtrandolapril in 1 trial.⁹¹ Valsartan was compared with lisinopril in 1 trial,⁸³ to benazepril in 2 trials,^{84, 105} and to ramipril in 2 trials.^{85, 95} Telmisartan was compared with enalapril in 1 trial⁸⁷ and irbesartan was compared with fosinopril in 1 trial.⁸⁶ We did not find any trials involving comparisons of either eprosartan or olmesartan to an ACE-I, or any trials involving comparisons of captopril, cilazapril, moexipril, or quinapril to an AIIRA.

One trial reported a renal survival outcome, including time to end stage renal disease or doubling of serum creatinine.⁸⁸ All but 2 trials compared the change in level or percent of proteinuria experienced; the 2 trials that did not report changes in proteinuria did report changes in renal function and were included for the benefit of those analyses.^{83, 94} Of note, while blood pressure control was not a primary outcome of interest in this analysis, blood pressure control is

known to impact proteinuria (with higher blood pressure leading to more proteinuria compared with lower blood pressure).¹⁰⁶ For that reason, if blood pressure control was reported as statistically not equivalent between groups, effects on proteinuria within that trial will not be considered to be independent of blood pressure control. No quality-of-life results were examined by any of these trials.

Of the 12 studies rated good or fair, only 1 showed that ACE-I was superior to AIIRA in its ability to reduce proteinuria independent of blood pressure control.⁸⁹ Two studies did not report proteinuria outcomes. Four studies did not report a statistical analysis comparing changes in proteinuria between groups,^{86, 90, 91, 102} but 2 of those did provide overlapping confidence intervals, suggesting no statistically significant difference.^{86, 90} The remaining 6 studies did provide statistical analysis comparing change in proteinuria between ACE-I and AIIRA groups and noted no statistically significant difference. In total, these data would suggest no additional benefit of ACE-I compared with AIIRA as monotherapy for the reduction of proteinuria in patients with proteinuric non-diabetic chronic kidney disease.

Losartan

Losartan compared with lisinopril

One trial compared the use of monotherapy with losartan compared with lisinopril for reduction of proteinuria (N=10).⁸⁹ This prospective open-label crossover study included 10 participants and provided 78 weeks of follow-up. We rated this study as fair based on small sample size and exclusion of 10% (1 of 10) of participants from final analysis. Participants had a range of different types of chronic kidney disease, including focal segmental glomerulosclerosis, membranous nephropathy, IgA nephropathy, and some with non-conclusive biopsies. All included participants were proteinuric (greater than 2 grams per day required with a median value of 4.5 grams per day) and had only modest declines in renal function (mean creatinine clearance was 80 ml/min at baseline). Escalating doses of each drug were used to determine the optimal antiproteinuric dose for each individual. Percent change in proteinuria based on use of that optimal antiproteinuric dose was compared.

Percent change in proteinuria was noted to be -75% (95% CI, -85 to -43) for lisinopril and -46% (95% CI, -60 to -24) for losartan. The notably broad confidence intervals likely stem from the very small sample size. This study did note a statistically greater decline in proteinuria for those on lisinopril compared with losartan ($P<0.05$). No statistically significant differences in changes in creatinine clearance were noted between groups. No outcomes involving mortality, hospitalization, cardiovascular events, or end stage renal disease were reported. No differences in blood pressure control between monotherapy groups were reported.

The rates of adverse events were similar for each therapy, with 10% (1 of 9) experiencing a potassium level of greater than 5.5 in the losartan group and 20% (2 of 9) experiencing a potassium level of greater than 5.5 in the lisinopril group; hyperkalemia was not a reason for withdrawal in either group. Similarly, 10% in each group (1 of 9) experienced dizziness while on therapy. No withdrawals due to adverse events were reported; the only withdrawal was related to non-adherence (specifically, inability to keep scheduled study appointments).

Losartan compared with enalapril

Losartan was compared with enalapril in 3 trials (N=145), all of which were conducted in Poland by the same group.^{93, 102, 103} All trials were rated fair quality. Losartan dose was 25 mg per day and enalapril dose was 10 mg per day in each trial. The trials ranged in duration from 3

months¹⁰³ to 12 months¹⁰² with 1 intermediate range of 9 months.⁹³ All 3 trials had a homogenous mix of participants including participants with mesangial glomerulonephritis, mesangiocapillary nephritis, and membranous nephropathy; 1 of these 3 trials also enrolled participants with focal segmental glomerulosclerosis.¹⁰³ Two trials specifically excluded participants with IgA nephropathy.^{102, 103} All included participants had baseline proteinuria levels that spanned similar values (1.8-3.2 g per day at baseline). Each trial required a creatinine of less than 2 mg/dL for inclusion, and all participants had a creatinine clearance of greater than 80 ml/min/1.73 m² at time of enrollment.

Effectiveness/efficacy outcomes. All 3 studies comparing losartan and enalapril (N=145) reported percent decrease in proteinuria after therapy.^{93, 102, 103} Renke and colleagues⁹³ reported percent decrease in proteinuria at 3 and 9 months as 26% and 44% for losartan and 43% and 50% for enalapril respectively. Tylicki and colleagues¹⁰³ reported percent decrease in proteinuria at 3 months of 25% for losartan and 45% for enalapril at 3 months. The difference between groups was found to not be statistically significant in either of these 2 trials ($P=0.09$ in Tylicki et al, and P value reported as not significant in Renke et al).^{93, 103} The third trial reported a 33% decline in proteinuria for those treated with losartan and a 41% decline for those treated with enalapril, but no statistical analysis was reported between these 2 groups.¹⁰² These 3 trials did not report outcomes on mortality, end stage renal disease, or quality of life.

One trial (N=51) reported percent decline in creatinine clearance for losartan compared with enalapril at 3 months.¹⁰³ The decline in creatinine clearance was noted to be greater in the enalapril (-15%) compared with the losartan group (percentage not reported), but the difference was not statistically significant ($P=0.09$).

Two trials (N=94) reported changes in creatinine clearance but only as compared with baseline, without inter-group comparisons.^{93, 102}

Two trials (N=91) showed comparable blood pressure control in each group.^{102, 103} One trial (N=54) showed slightly lower diastolic blood pressures among those treated with losartan compared with enalapril ($P=0.04$), but that difference was noted only at 3 months.⁹³ All 3 studies reported overall withdrawals, but those withdrawals were not consistently broken down by study groups, limiting the ability to make inter-group comparisons.

One study reported a subgroup analysis comparing the effect of losartan therapy on participants delineated by baseline proteinuria level (greater than or less than 1.5 grams per day of proteinuria at baseline).¹⁰² This trial also reported changes in proteinuria between 2 varied doses of losartan; as neither of these subgroups addressed a comparison question between ACE-I and AIIRA, those results will not be discussed here, but details are available in Evidence Table 9.

Harms. Information on harms was not reported these 3 studies with the exception of the withdrawals related to allergic reactions. Each trial reported 1 withdrawal related to allergic reaction to study medication, but which medication was not specified.

Losartan compared with benazepril

Losartan was compared with benazepril in 3 trials (N=420) conducted in China⁸⁸ and Poland.^{94, 104} Two were rated fair quality^{94, 104} and 1 was rated good quality.⁸⁸ The Reno protection of Optimal Antiproteinuric Doses (ROAD) study by Hou and colleagues is notable as the largest and longest duration trial comparing monotherapy with AIIRA compared with ACE-I with 360 participants and 3 years follow-up. The 2 remaining trials followed participants for 5 months⁹⁴ and 20 months¹⁰⁴ and had 30 participants each. These trials were produced by the same research

group in Poland. Two trials used doses of benazepril 10mg daily and losartan 50mg daily exclusively,^{94, 104} while 1 used benazepril 10 mg daily and losartan 50 mg daily as starting doses, but also included escalating doses to maximum of benazepril 40 mg daily and losartan 200 mg daily.⁸⁸ Two of these 3 trials were homogeneous in terms of participants^{94, 104} and enrolled participants with mesangial glomerulonephritis, mesangiocapillary glomerulonephritis, IgA nephropathy, and membranous nephropathy. The 1 remaining trial included a different range of chronic kidney disease, and enrolled participants with glomerulonephritis, polycystic kidney disease, hypertensive renal disease, interstitial renal disease, and those with renal disease of unknown etiology.⁸⁸ Two trials included participants with relatively normal renal function (mean baseline creatinine clearance greater than 80 ml/min/1.73 m²),^{94, 104} while the remaining study enrolled participants with baseline mean estimated glomerular filtration rates of approximately 30 ml/min/1.73 m².⁸⁸ All participants were required to have proteinuria at the time of enrollment; baseline proteinuria was approximately 2 grams per day on average in all 3 studies.

Effectiveness/efficacy outcomes. A trial (N=360) conducted at a single center in China reported a composite outcome of death, end stage renal disease, and doubling of serum creatinine over 3 years of follow-up.⁸⁸ This trial was unique in that half of its participants were randomized to benazepril 10 mg daily compared with losartan 50 mg daily, while the other half were randomized to “maximum” dose groups of benazepril and losartan. In the “maximum” dose groups, doses were titrated to the dose at which each individual achieved optimal antiproteinuric efficacy (as high as benazepril 40 mg daily and losartan 200 mg daily). There was no significant difference for percent reduction in the primary endpoint for losartan compared with benazepril at any dose (*P* values not reported), but a statistically significant lower percentage of participants reached the primary endpoint in each “maximum” group compared with group on the lower dosage of the same medication.

Two trials (N=60) conducted at the University of Gdansk in Poland reported whether or not change in creatinine clearance was significant as compared with baseline (*P* values not reported).^{94, 104} After 5 months, Renke and colleagues found no significant difference in creatinine clearance between groups (*P* values not reported). In the study by Rutkowski and colleagues, after 14 months no significant change in creatinine clearance was seen between groups or compared with baseline.

One group (N=30) reported percent decline in proteinuria from baseline.¹⁰⁴ They noted a numerically greater percent decline in proteinuria for losartan compared with benazepril, but that difference was not statistically significant (*P*=0.093). One group (N=360) reported only that change in proteinuria was not statistically significant between losartan and benazepril treatment groups.⁸⁸ Raw numbers were not provided for proteinuria changes, so no rough percent change was calculated. One group did not report reduction in proteinuria for monotherapy comparisons.⁹⁴

There were no significant differences in blood pressure control between treatment arms in either study. One study did perform a subgroup analysis examining reduction in proteinuria for those participants who started with baseline proteinuria of greater than or less than 2 grams per day.¹⁰⁴ Those with proteinuria of greater than 2 grams per day showed significantly greater reduction in comparison with those with less than 2 grams per day proteinuria at baseline (*P*=0.0026 for losartan and *P*=0.019 for benazepril).

Two trials reported overall withdrawals, but did not break down those withdrawals by treatment group.^{94, 104} This trial noted a 23% to 25% withdrawal rate in the 2 benazepril groups, compared with a 6% withdrawal rate in the 2 losartan groups. The majority of those withdrawals

in the benazepril groups were related to cough; if the withdrawal rate for the benazepril groups is calculated excluding withdrawals for cough, then the withdrawal rate ranges from 4% to 8%.

Harms. One trial reported overall harms delineated by treatment groups; this study noted equivalent rates of hyperkalemia between groups, but a differential rate of cough. They described a statistically greater occurrence of cough in the benazepril arm compared with the losartan arm (*P* value not reported).⁸⁸ In the trial of 5-month duration, information on harms noted 2 hypotensive events, 1 allergic reaction to losartan, and 1 participant with cough, but these harms were not clearly delineated by treatment groups.⁹⁴ Similarly, the 14-month study reported 2 instances of cough and 2 instances of documented hypotension, but those harms were again not clearly delineated by treatment groups.¹⁰⁴

Losartan compared with trandolapril

Losartan was compared with trandolapril in 1 trial (N=62), which was conducted in Japan and was rated fair quality.⁹¹ This trial provided 2 years of follow-up.⁹¹ Participants included in this trial had specific types of glomerulonephritis including proliferative glomerulonephritis, membranous glomerulonephritis, and focal segmental glomerulosclerosis.⁹¹ The mean creatinine clearance in this study was greater than 80ml/min/1.73 m², with baseline proteinuria of approximately 2.5 grams/24 hours. Losartan dose was 25 mg daily, compared with a trandolapril dose of 0.5 mg per day.

This trial did not report a composite renal endpoint or renal survival endpoint, but did report percent decrease in proteinuria compared with baseline at 12 and 96 weeks. Both losartan (-12% and -36% at 12 and 96 weeks respectively) and trandolapril (-38% and -54% at 12 and 96 weeks respectively) showed statistically significant declines in proteinuria within each group at each time point compared with baseline, but no inter-group comparisons were made. This trial also reported changes in creatinine clearance over the course of the study; no significant effect on creatinine clearance with ACEI compared with AIIRA was noted (statistical analysis was not provided). There were no significant differences in blood pressure control between treatment arms.

This study did not report withdrawals of study participants or specific harms.

Losartan compared with perindopril

Losartan was compared with perindopril in 1 randomized controlled trial, which concurrently compared losartan to trandolapril and is described above.⁹¹ Doses of drugs for comparisons included losartan 25 mg per day and perindopril 2 mg per day.

All treatment groups showed significant decline in proteinuria compared with baseline at 12 and 96 weeks, but no inter-group statistical comparisons are reported. The losartan group showed a 12% and 36% reduction in proteinuria at 12 and 96 weeks respectively compared with a 47% and 61% reduction at 12 and 96 weeks respectively in the perindopril group. Creatinine clearance did not change significantly from baseline in any groups. No significant differences in blood pressure control were noted between groups.

Withdrawals and harms were not reported for this trial.

Candesartan

Candesartan compared with lisinopril

Candesartan was compared with lisinopril in 1 multicenter randomized active control parallel group trial, which included 46 participants recruited from 7 centers across Spain with 24 weeks

of follow-up.⁹⁰ This trial was rated fair quality due to its small sample size and the fact that adverse events were not delineated by treatment groups. Beginning doses of candesartan and Lisinopril were 8 mg daily and 10 mg daily respectively, but those doses were increased as needed to achieve blood pressure control of less than 125/75 mmHg (possible maximum doses of 32 mg daily and 40 mg daily respectively). Participants enrolled in this study all had proteinuria of greater than 2 grams per day; specific types of chronic kidney disease among participants were not reported, but mean baseline creatinine clearance ranged from 84-100 ml/min/1.73 m².

Change in urinary protein to creatinine ratio as a quantification of proteinuria was the primary outcome of interest. Percent reduction in proteinuria was noted at 2, 3, and at 6 months for each treatment group (only 6 months are discussed here; reduction seen throughout the study. See Evidence Table 9 for complete details). For lisinopril, percent reduction was -50% at 6 months (95% CI, -9 to -90; $P=0.019$ compared with baseline). For losartan, percent reduction in proteinuria was -48% at 6 months (95% CI, -32 to -63; $P<0.001$ compared with baseline). Statistical analysis was not reported between monotherapy groups; given the overlap in confidence intervals, presumably no statistically significant difference exists between groups. There was no statistically significant difference in blood pressure control between groups. There was no significant difference in creatinine clearance between groups.

Only 1 withdrawal was reported for this study, and that was specifically reported as not being related to adverse events. A total of 8 hyperkalemia events with values greater than 5.5 milli-equivalents per liter were reported; those events were not reported by treatment group. This trial did note that those treated with candesartan were statistically ($P<0.001$) less likely to experience a potassium level of greater than 5.5 milli-equivalents per liter compared with participants on lisinopril or participants in the combination therapy arm (described below).

Candesartan compared with perindopril and trandolapril

Candesartan was compared with perindopril and trandolapril in a single randomized controlled trial, and will be discussed together.⁹¹ This study also compared losartan to perindopril and trandolapril and is described above. Comparison doses were candesartan 4 mg per day, perindopril 2 mg per day, and trandolapril 0.5 mg per day. All treatment groups showed significant decline in proteinuria compared with baseline at 1 and 96 weeks. Only the 12-week percent decline was reported for candesartan (38%), but that anti-proteinuric effect was reported as being “sustained” throughout the duration of the study. The perindopril group experienced -43% and -61% declines in proteinuria at 12 and 96 weeks respectively and the trandolapril group experienced -38% and -54% declines in proteinuria at 12 and 96 weeks respectively. No inter-group statistical comparisons are reported between these therapies. Blood pressure control was reported to statistically the same between groups, and no statistically significant change in creatinine clearance was noted during the study.

Withdrawals and adverse events were not reported for this trial.

Valsartan

Valsartan compared with lisinopril

Valsartan was compared with lisinopril in 1 multi-center randomized double-crossover study across 5 states in the United States.⁸³ This study included 37 participants, all of whom had chronic kidney disease, although the types of chronic kidney diseases among participants were not reported. The duration of follow-up was 12 weeks. Participants were randomized to valsartan 80 mg daily or lisinopril 10 mg daily, and were crossed over into each treatment arm after an

intervening washout period. This study was rated as fair due to small sample size and lack of adverse event reporting. Proteinuria among participants was not reported. Doses of comparison medications included lisinopril 10 mg per day and valsartan 80 mg per day.

The primary and secondary endpoints of this trial were not concordant with topics of interest for our review (change in serum potassium with an AIIRA compared with an ACE-I, serum aldosterone and renin levels on an AIIRA compared with an ACE-I), but this study did examine changes in glomerular filtration rates on these therapies. Calculations based on provided glomerular filtration rate values showed a rough 4% increase in glomerular filtration rate for those treated with losartan compared with a 3% decline in glomerular filtration rate for those treated with valsartan. No significant change in glomerular filtration rate compared with baseline was noted in either arm after completion of therapy, and no statistical analysis between groups was reported. Blood pressure decline was noted to be similar in each group, although statistical analysis on blood pressure decline was not reported. A subgroup analysis was done by dividing participants into those with estimated glomerular filtration rate of greater compared with less than 60 ml/min/1.73 m², but no outcomes of interest were examined within these subgroups.

Two participants were withdrawn from this study, but reason for withdrawal was not reported. The number of hyperkalemic events was not reported, but authors did note a statistically significant difference in potassium levels between treatment arms.

Valsartan compared with benazepril

Valsartan was compared with benazepril in 2 studies (N=60), which took place in Italy⁸⁴ and Spain.¹⁰⁵ Both studies were rated fair quality. Both studies compared escalating doses of valsartan (80 mg then increased to 160 mg daily) and benazepril (10 mg then increased to 20 mg daily), although 1 study limited benazepril 20 mg daily to those with creatinine clearance greater than 50 ml/min.¹⁰⁵ These 2 trials were heterogeneous in terms of participant characteristics and types of chronic kidney disease. Follow-up was 6 months in 1 trial¹⁰⁵ and 32 weeks in the other.⁸⁴ One trial enrolled participants with chronic glomerulonephritis, IgA nephropathy, and “other” types of renal disease (biopsy was not required),⁸⁴ while the other did not report types of chronic kidney disease in their participants. Both studies required participants to be proteinuric; baseline proteinuria levels were 3 grams per day in 1 trial⁸⁴ and ranged from 3.8-4.6 grams per day in the other trial.¹⁰⁵ Both trials also included participants with similar baseline creatinine clearance values (69-74 ml/min on average). Doses of compared medications did differ between these trials; 1 trial used benazepril 10 mg per day and valsartan 80 mg per day,⁸⁴ and the other used either benazepril 10 or 20 mg per day (depending on level of creatinine clearance) and valsartan starting at 80 mg per day but then increased to 160 mg per day.¹⁰⁵

Effectiveness/efficacy outcomes. Two studies reported overall changes in proteinuria from baseline. One study reported percent reduction in proteinuria compared with baseline, and values appeared numerically similar between groups (–41% and –45% for valsartan and benazepril respectively).⁸⁴ No statistically significant difference in proteinuria reduction was noted between valsartan and benazepril therapy. The other trial reported mean decreases in proteinuria as 0.5 +/- 1.7 grams per day for benazepril and 1.2 +/- 2 grams per day for valsartan rough calculation of mean percent decline in proteinuria using these numbers shows –13% for benazepril and –26% for valsartan. Although this percent change does appear numerically different, no statistically significant difference was found between these groups.¹⁰⁵ Neither of these 2 trials reported mortality, end stage renal disease, or quality of life outcomes.

One study reported changes in creatinine clearance and glomerular filtration rate compared with baseline.⁸⁴ Creatinine clearance and glomerular filtration rate numerically remained relatively unchanged in both treatment groups, but no statistical analysis of this change was reported. The other study did not report changes in creatinine clearance or glomerular filtration rate.¹⁰⁵

Campbell and colleagues found no statistically significant differences in blood pressure management in either treatment group. Segura and colleagues, however, found that systolic blood pressure was significantly lower in the valsartan group compared with the benazepril group at 3 and 6 months. One study reported no withdrawals,⁸⁴ and the other study did not provide information on withdrawals.¹⁰⁵

Harms. Information on harms was reported in 1 of these 2 trials.⁸⁴ Campbell and colleagues looked specifically for potassium levels greater than 0.5 milli-equivalents per liter above baseline; this adverse event was not noted in any treatment groups. No additional adverse events were reported.

Valsartan compared with ramipril

Valsartan was compared with ramipril in 2 trials (N=98) conducted in France⁸⁵ and Sweden.⁹⁵ Both studies were rated as fair. Both trials included a variety of types of chronic kidney disease with some overlap between trials; types of chronic kidney disease of participants included diabetic nephropathy, focal segmental glomerulosclerosis, IgA nephropathy, minimal change disease, amyloidosis, and mesangioproliferative glomerulonephritis in 1,⁸⁵ and focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis, hypertensive nephrosclerosis, and minimal mesangial proliferation in the other.⁹⁵ Both studies required participants to have proteinuria; baseline proteinuria among participants varied from 1.5 grams per day⁹⁵ to 3.7 grams per day.⁸⁵ One trial delineated participants by creatinine, requiring creatinine less than 2.8 mg/dL for inclusion.⁸⁵ The other study delineated participants by glomerular filtration rate, requiring a range from 30-59 ml/min/1.73 m² for inclusion.⁹⁵ Both trials used valsartan 160 mg daily as their treatment dose, but ramipril doses ranged from 5 mg daily⁹⁵ to 10 mg daily.⁸⁵

Effectiveness/efficacy outcomes. Neither of these 2 trials reported mortality, end stage renal disease, or quality of life outcomes.

Both trials reported changes in proteinuria among participants receiving these 2 treatments. One group examined both mean protein to creatinine ratio and mean proteinuria on 24 hour urine collection after treatment.⁸⁵ They found no statistically significant difference in either of these measures between valsartan and ramipril. This trial additionally reported no significant differences in blood pressures between treatment groups. The other study examined changes in proteinuria by examining pre and post treatment proteinuria values.⁹⁵ In their analysis they noted a more significant decline in proteinuria with ramipril (-53% change) compared with valsartan (-38%) ($P=0.02$). Within that study, however, systolic blood pressure and diastolic blood pressure were also significantly lower in the ramipril group as compared with the valsartan group ($P=0.007$ for systolic and $P=0.001$ for diastolic blood pressure differences between groups), so the anti-proteinuric effects noted may not be independent of blood pressure.

Both trials reported outcomes in terms of renal function, 1 group via serum creatinine⁸⁵ and 1 via glomerular filtration rate.⁹⁵ Esnault and colleagues found no significant differences in serum creatinine levels after treatment with either valsartan or ramipril. Yilmaz and colleagues

similarly found no significant difference in pre and post treatment glomerular filtration rate among those treated with valsartan compared with ramipril.

One trial did report a subgroup analysis examining antiproteinuric outcomes among diabetics compared with non-diabetics. Diabetics were found to have a statistically greater degree of proteinuria at baseline compared with non-diabetics ($P=0.033$). No significant difference in reduction in protein to creatinine ratio was found comparing any treatment groups within this diabetic subgroup.

Both studies reported withdrawals. One study reported 14 withdrawals, all of which were related to adverse events⁹⁵; the remaining study reported 2 withdrawals, 1 of which was related to an adverse event.⁸⁵

Harms. Adverse events were reported by both trials. One trial looked specifically for hypotension, and they note that there was no difference in the number of occurrences of hypotensive events within each treatment arm (specific numbers of events and statistical analysis are not reported).⁸⁵ That group additionally reported 1 event of laryngeal edema with ACE-I. The remaining trial noted 8 adverse events in the ramipril group and 6 adverse events in the valsartan group, but specific types of adverse events were not delineated by group.⁹⁵

Telmisartan

Telmisartan compared with enalapril

One multi-center trial from France compared telmisartan to enalapril (N=71).⁸⁷ This double-dummy, parallel group, active control trial received a quality rating of fair and followed participants for 12 weeks. Participants were required to have a creatinine clearance of between 30-80 ml/min (average at baseline was 50 ml/min), but types of chronic kidney disease among participants were not reported. Baseline proteinuria among participants ranged from 1.6-2.4 grams per day. Starting doses of telmisartan 40 mg daily and enalapril 10 mg daily were utilized, with dose increase to telmisartan 80 mg daily and enalapril 20 mg daily if diastolic blood pressure remained between 90-110 mmHg. If diastolic blood pressure remained elevated on maximum dose of study medication, then furosemide could be added as a once daily dose of 40 mg.

Eligible efficacy/effectiveness outcomes from this study included changes in creatinine clearance and proteinuria. Mean change in proteinuria between those treated with telmisartan (-26.5%) compared with enalapril (-57.2%) were numerically different, but that difference was not statistically significant ($P=0.14$). Median percent decline in creatinine clearance also showed no statistically significant difference between groups. Blood pressure control was statistically similar between groups. 57 participants completed this protocol; there were 10 withdrawals (6 of which were reported as being related to adverse events).

Harms were reported for multiple categories, but no statistical analysis comparing groups was reported. Hypotension, dizziness, asthenia, pain, cough, uremia, and dysuria each reported zero to 1 event for telmisartan and enalapril. Abdominal pain and nausea was reported 4 times for enalapril, compared with zero times for telmisartan. Additionally, 2 withdrawals for acute renal failure were reported; treatment groups for that adverse event were not specified.

Irbesartan

Irbesartan compared with fosinopril

One single-center study in Switzerland compared the use of irbesartan to fosinopril (N=11).⁸⁶ This study received a quality rating of fair, and followed participants for 32 weeks. Participants

had a range of glomerulonephritides including focal segmental glomerulosclerosis, IgA nephropathy and membranoproliferative glomerulonephritis and were required to have proteinuria of greater than 1.5 grams per day. The baseline mean creatinine clearance at baseline was 77 ml/min. This trial utilized fosinopril at 20 mg per day and irbesartan at 150 mg per day; additional diuretics were allowed if needed for edema management.

The only eligibility/efficacy outcome of interest reported from this study was percent decline in proteinuria. Participants in the irbesartan group were noted to have a 37% decline in proteinuria (from 7.9 +/- 7.2 grams per day to 5.0 +/- 4.9 grams per day, while those in the fosinopril group were noted to have a 33% decline in proteinuria (from 7.9 +/- 7.2 grams per day to 5.3 +/- 5.2 grams per day). No statistical analysis comparing changes in proteinuria between groups was reported, but confidence intervals are noted to overlap suggesting no significant difference between groups (although this may also be influenced by very small sample size). Change in creatinine clearance was not reported. There were no statistically significant differences in blood pressure control between groups. This trial did report 1 withdrawal, which was not related to an adverse event.

This trial reported adverse events by treatment groups, but did not provide statistical analysis for comparison between groups. No participants in the fosinopril or irbesartan arm experienced either cough or dizziness. Two participants in the fosinopril group experienced acute renal failure, compared with zero in the irbesartan group. Two in the fosinopril group experienced a potassium level greater than 5 milli-equivalents per liter, as compared with only 1 in the irbesartan group.

Combination therapy: Inter-class comparison of effectiveness, efficacy and harms between AIIRA and ACE-I

Proteinuric Chronic Kidney Disease

We included 16 trials that compared the combination of an AIIRA and an ACE-I with either or both as monotherapy.^{84-86, 89, 90, 93, 94, 103-105, 107-112} Four trials were rated poor quality and will not be discussed in this analysis, but additional information can be found in Evidence Table 10.^{92, 96, 98, 113} Two of these 4 trials, Kahvecioglu and colleagues and Russo and colleagues, were rated poorly due to very high withdrawal rates of 32% and 49% respectively.^{98, 113} The former provided no significant information on adverse events;¹¹³ the latter had a very small sample size (19, nine of whom withdrew).⁹⁸ The COOPERATE trial and its sub-study were rated as poor for reasons discussed previously.^{92, 96} The majority of trials (11 of 16) provided 6 months or more of follow-up^{84-86, 89, 90, 93, 104, 105, 109, 110, 112}, the longest of which was 36 months (3 years).¹¹¹ Only 4 of 16 trials had sample sizes of fifty or greater,^{93, 103, 110, 111} the largest of which was 109 participants.¹¹¹ Four trials had fewer than twenty participants.^{85, 86, 89, 107} Participants among these 16 trials had a wide range of different types of chronic kidney disease.

None of these studies reported a renal survival endpoint. One trial reported a renal outcome endpoint including acute kidney injury and hospitalization for renal-related issues.¹¹¹ All trials reported changes in levels of proteinuria with combination compared with monotherapy with AIIRA and ACE-I. Of note, although the reduction of proteinuria among patients with chronic kidney disease has been linked to a slowing in disease progression,¹¹⁴⁻¹¹⁷ reduction in proteinuria is a surrogate outcome for renal survival. All trials reported changes in creatinine clearance or estimated glomerular filtration rate with the exception of 2 that reported changes in creatinine^{107, 111} and 1 that did not report renal function measurement outcomes.¹⁰⁵

These 16 trials have some fundamental differences in design which complicate interpretation for an overall effect of mono compared with combination therapy on proteinuria and renal function. The 2 primary designs were those trials in which ACE-I and AIIRA combination therapy was simultaneously compared with monotherapy with either agent, compared with those trials in which monotherapy of either ACE-I or AIIRA were compared with combination therapy. Those trials comparing monotherapy of 1 agent (ACE-I or AIIRA) to combination therapy typically started with all patients on monotherapy and added a second agent compared with placebo to result in a combination therapy arm. Ten trials compared both ACE-I and AIIRA monotherapy with combination therapy,^{84-86, 89, 90, 93, 94, 103-105} and 6 trials compared monotherapy of either ACE-I or AIIRA to combination therapy.¹⁰⁷⁻¹¹²

Another design difference was noted in drug dosing. Among those trials comparing monotherapy of both agents with combination therapy, authors either utilized same dose ACE-I and AIIRA in mono and combination therapy or they utilized half dose ACE-I and AIIRA in combination therapy compared with double that dose in monotherapy. Of those comparing dual monotherapy to combination therapy, 5 used same dose ACE-I and AIIRA in both mono and combo therapy,^{86, 89, 93, 103, 105} and 5 used half dose ACE-I and AIIRA in combination therapy compared with double that dose in monotherapy.^{84, 85, 90, 94, 104}

The trials comparing monotherapy of ACE-I and AIIRA compared with combination therapy were varied in their effects on proteinuria. Nine of these 11 trials noted a significant reduction in proteinuria with combination compared with monotherapy, but only 5 showed that effect as independent of blood pressure. Of the 5 trials using equivalent doses in mono and combo therapy, only 1 of the 5 showed that combination therapy was superior to either monotherapy for reduction in proteinuria independent of blood pressure control.⁸⁶ Of the 5 trials that compared half dose combination therapy to double that dose monotherapy, 3 of the 5 showed significant reduction in proteinuria with combination therapy that was independent of blood pressure control.^{84, 94, 104}

Of the 6 trials designed with all participants on monotherapy with ACE-I or AIIRA followed by the addition of the other type of agent compared with placebo, only 2 of the 6 showed a clear and significantly greater reduction in proteinuria for combination therapy compared with monotherapy.^{109, 110} Further, in the trial by Kim and colleagues, subgroup analysis only showed significantly greater reduction in proteinuria with combination therapy among those with IgA nephropathy, and not among those with diabetic nephropathy. Similarly, another trial among these 6 also showed a significant reduction in 1 subgroup of chronic kidney disease patients (IgA nephropathy), but not in another included subgroup (diabetic nephropathy).¹¹² A fourth trial within this group showed a significantly greater reduction in proteinuria in combination therapy compared with monotherapy, but only with the highest dose of combination therapy (whereas a group with lower dose combination therapy did not reveal a statistically significant decrease in proteinuria compared with monotherapy).¹¹¹

In total, only 4 of 16 studies found a statistically significantly greater reduction in proteinuria among those on combination therapy with ACE-I and AIIRA compared with monotherapy with either agent that was independent of blood pressure management. These studies suggest do not provide consistent and convincing data regarding the reduction in proteinuria with combination compared with monotherapy with these agents.

Monotherapy with ACE-I and AIIRA compared with combination therapy

Losartan

Losartan in combination with lisinopril

One trial (N=10) compared the effects of combination therapy using losartan and lisinopril to monotherapy with losartan or lisinopril on reduction in proteinuria and changes in creatinine clearance.⁸⁹ Details of this trial are discussed previously. Participants were randomized to escalating doses of lisinopril or losartan in order to identify the optimal antiproteinuric dose for each participant. Participants were then crossed-over the alternate agent and the same process was repeated. After the optimal antiproteinuric dose of ACE-I and AIIRA was identified for each participant, all participants were placed on combination therapy of both agents at their optimal antiproteinuric dose.

This trial showed a 51% reduction in proteinuria for those on losartan alone, a 69% reduction in proteinuria for those on lisinopril alone, and a 78% reduction in proteinuria for those on combination therapy at optimal antiproteinuric doses. Reduction in proteinuria with combination therapy was found to be significantly greater ($P<0.05$) compared with either monotherapy. Combination therapy was also noted to lower blood pressure significantly more than losartan monotherapy. Changes in creatinine clearance compared with baseline were not statistically significant for either monotherapy, but were statistically significantly lower among those on combination therapy ($P<0.05$). This trial reported 1 withdrawal, which was not related to adverse events.

Two adverse events were reported for each therapy arm in this trial: the incidence of potassium levels greater than 5.5 milli-equivalents per liter and the incidence of dizziness. Two participants experienced both elevated potassium and dizziness in the combination therapy group (20% event rate for each adverse event). Losartan monotherapy resulted in a 10% adverse event rate for each adverse event (meaning 1 participant for each), and lisinopril monotherapy resulted in a 20% event rate for hyperkalemia (2 participants) and a 10% event rate for dizziness (1 participant). None of these adverse events resulted in a withdrawal of therapy.

Losartan in combination with enalapril

Two trials compared the combination of losartan plus enalapril to monotherapy with either losartan or enalapril (N=105).^{93, 103} Complete details of both of these trials are discussed previously and can also be seen in Evidence Table 9. Both trials compared monotherapy with losartan 25 mg per day or enalapril 10 mg per day to combination therapy with losartan 25 mg per day plus enalapril 10 mg per day.

Effectiveness/efficacy outcomes. Despite significant similarities in design, these trials resulted in different outcomes. In the trial with shorter duration of follow-up (N=51), combination therapy resulted in a 66% reduction in proteinuria, as compared with a 25% reduction in proteinuria for losartan monotherapy and a 45% reduction in proteinuria for enalapril monotherapy.¹⁰³ Reduction in proteinuria was found to be statistically greater among those on combination therapy when compared with either monotherapy ($P=0.009$) at the end of the 3-month follow-up. No significant changes were found in creatinine clearance. Of note, diastolic blood pressure was lower among those on combination therapy.

In the trial with longer duration follow-up (N=54), combination therapy resulted in a 63% and 51% decline in proteinuria at 3 and 9 months respectively. Losartan monotherapy resulted in

a 22.6% and 44.2% decline in proteinuria, and enalapril resulted in a 43.1% and 49.6% decline in proteinuria both at 3 and 9 months respectively. A statistically significant difference was seen only between combination therapy and losartan monotherapy ($P<0.01$) and only at 3 months. No statistically significant difference in reduction of proteinuria was seen between groups at 9 months. There was no statistically significant change in creatinine clearance between groups. There were some statistically significant differences in diastolic blood pressure levels between groups (lower among those on losartan but only at 3 months, $P=0.04$ and lower among those receiving combination therapy as compared with enalapril monotherapy, $P=0.009$). Each trial reported 2 withdrawals.

Harms. One trial did not report adverse events.⁹³ The other trial reported 1 allergic reaction to a study medication, but they did not report which medication led to that reaction.¹⁰³

Losartan in combination with benazepril

Two trials compared the combination of losartan with benazepril to monotherapy with either agent ($N=60$).^{94,104} Complete details on both of these studies are discussed earlier, and can also be found in Evidence Table 9. Both studies utilized the same doses of each medication: Losartan 50 mg per day, compared with benazepril 10 mg per day, compared with half dose combination therapy (losartan 25 mg per day with benazepril 5 mg per day).

Effectiveness/efficacy outcomes. These studies resulted in similar results in terms of reduction of proteinuria. In the trial with shorter duration of follow-up ($N=30$), a significantly greater reduction in proteinuria was seen in those on combination therapy as compared with either monotherapy ($P<0.01$ for each group, total percent reduction not reported).⁹⁴ The other trial with longer duration of follow-up ($N=30$) also showed a 45.5% reduction in proteinuria for those on combination therapy, compared with a 28% and 20% reduction in proteinuria for those on losartan and benazepril monotherapy respectively.¹⁰⁴ Analysis revealed a statistically greater reduction in proteinuria in those on combination therapy compared with losartan monotherapy ($P=0.009$) and compared with benazepril monotherapy ($P<0.01$). Neither trial found a significant change in creatinine clearance; both trials reported equivalent blood pressure control between groups. Each trial reported 6 withdrawals.

Harms. Each trial reported a total number of adverse events, but neither trial delineated those events by treatment group.

Candesartan

Candesartan in combination with lisinopril

One randomized controlled trial from Spain ($N=46$) compared the use combination therapy candesartan and lisinopril to monotherapy of either agent in its effect on proteinuria and creatinine clearance.⁹⁰ Details of this trial are discussed earlier in this document. This trial compared lisinopril 10 mg daily or candesartan 8 mg daily to half dose combination therapy (lisinopril 5 mg daily with candesartan 4 mg daily). Percent reductions in proteinuria were reported at 2, 3, and 6 months. See Evidence Table 9 for all reported values. At 2 and 6 months, combination therapy resulted in 60 and 70% reduction in proteinuria respectively. This was found to be a statistically greater reduction compared with candesartan monotherapy at both time points (28% reduction with candesartan at 2 months [$P=0.019$; 95% CI, -45 to +12] and 48%

reduction at 6 months [$P<0.001$; 95% CI, -32 to -63]). Compared with lisinopril monotherapy, however, reduction in proteinuria with combination therapy was only statistically greater at 2 months (33% reduction at 2 months [$P=0.008$; 95% CI, -12 to -56] and 55% reduction at 6 months [$P=0.013$; 95% CI, -9 to -90]). This trial reported no significant changes in creatinine clearance and blood pressures were equivalent between groups. One participant was withdrawn from this study. The adverse event of potassium level greater than 5.5 milli-equivalents per liter was reported, but reporting was not delineated by treatment groups. Authors did note that significantly more participants in lisinopril monotherapy and lisinopril with candesartan combination therapy experienced a potassium level greater than 5.5 milli-equivalents per liter as compared with those on candesartan monotherapy ($P<0.001$).

Valsartan

Valsartan in combination with benazepril

Two trials (N=60) compared the use of valsartan and benazepril combination therapy to either agent as monotherapy for its impact on proteinuria and renal function.^{84, 105} For complete details of these studies please see discussion above or data presented in Evidence Table 9. Doses of medications differed some between these 2 studies. One trial utilized valsartan 80 mg per day and benazepril 10 mg per day for monotherapy, but used half dose for combination therapy (valsartan 40 mg per day and benazepril 5 mg per day) again dose doubled among all groups after 2 weeks.⁸⁴ The other used a benazepril dose based on creatinine clearance (10 mg per day if creatinine clearance was less than 50 ml/min and 20 mg per day if creatinine clearance was greater than 50 ml/min) for ACE-I monotherapy, valsartan 80 mg per day with later dose escalation for AIIRA monotherapy, and maximum dose of each for combination therapy.¹⁰⁵

Effectiveness/efficacy outcomes. Both trials reported changes in proteinuria. In the trial using half-dose combination therapy, the authors noted a statistically greater decline in proteinuria among those on combination therapy compared with monotherapy after 32 weeks (-56% for combination compared with -41%; $P<0.05$ and -45%; $P<0.01$ for valsartan and benazepril respectively).⁸⁴ There was no significant difference in blood pressure control between groups in this study. In the trial using same dose monotherapy compared with combination therapy, combination therapy resulted in a statistically greater decline in proteinuria only when compared with benazepril monotherapy ($P<0.05$), but results comparing combination therapy to losartan monotherapy did not show a statistically significant difference.¹⁰⁵ Of note, systolic blood pressure in this trial was noted to be lower in the valsartan compared with the benazepril group at 3 and 6 months, so the changes in proteinuria cannot necessarily be considered to be independent of blood pressure. Campbell and colleagues additionally reported slight increase in estimated glomerular filtration rate for those on combination therapy that was statistically greater when compared with either monotherapy ($P=0.04$ for valsartan and $P=0.048$ for benazepril); there was no statistically significant difference between levels of creatinine clearance between combination and monotherapy in this trial.⁸⁴ Segura and colleagues did not report on changes in creatinine clearance.¹⁰⁵

Harms. One trial evaluated participants for the adverse event of potassium level greater than 0.5 milli-equivalents per liter above baseline; they found no adverse events throughout their trial.⁸⁴

Valsartan in combination with ramipril

One study (N=18) evaluated the use of valsartan in combination with fosinopril to examine the impact of these therapies on proteinuria reduction.⁸⁵ Complete details of this study are discussed previously in this document, and are also available in Evidence Table 9. Participants in this study were randomized to valsartan 160 mg per day or ramipril 10 mg per day for monotherapy, compared with half dose combination therapy (valsartan 80 mg per day with ramipril 5 mg per day). This trial reported changes in the protein to creatinine ratio as well as the 24 hour protein levels. No significant difference in reduction in proteinuria was seen between combination and monotherapy. Creatinine levels were followed and were not found to differ significantly between groups before and after intervention. Blood pressure control between groups was equivalent. *As noted previously, a subgroup analysis was done within this trial comparing participants with and without diabetes. Although, as previously noted, no statistically significant difference was seen between groups, there was a trend toward combination therapy leading to a greater reduction in proteinuria compared with monotherapy in diabetics (P=0.08).* Two participants were withdrawn from this study. Adverse events are mentioned solely in terms of hypotension, and no difference in episodes of symptomatic hypotension was found between treatment groups.

Irbesartan

Irbesartan in combination with fosinopril

One trial compared the use of irbesartan in combination with fosinopril to monotherapy with either agent and examined outcomes of proteinuria reduction and renal function.⁸⁶ Details of this study are reviewed previously in this document, but are notable for a very small sample size (N=11). Participants were randomized to irbesartan 150 mg per day or fosinopril 20 mg per day for monotherapy compared with full dose combination therapy (irbesartan 150 mg per day with fosinopril 20 mg per day). This trial found that combination therapy lowered proteinuria significantly more than either monotherapy alone (–58% in combination therapy compared with –33% and –37% for fosinopril and irbesartan monotherapy respectively, $P=0.039$). Creatinine clearance was reported as remaining stable throughout this study; no difference in blood pressure control between groups was found. Authors reported 1 withdrawal from this trial. A variety of adverse events were followed, including transient dizziness, cough, reversible increase in serum creatinine, and serum potassium greater than 5 millimoles per liter. The number of participants in combination therapy who experienced transient dizziness (2) was greater than that noted for monotherapy (zero for both monotherapy groups). The number of participants in combination therapy who experienced serum potassium greater than 5 millimoles per liter (2) was greater than those in the irbesartan group (1), but the same as those in the fosinopril group (2). Statistical analysis of adverse events rates was not provided.

Combination therapy with ACE-I and AIIRA compared with monotherapy with ACE-I or AIIRA

ACE-I and AIIRA compared with ACE-I alone

Losartan and lisinopril compared with lisinopril alone

One trial compared the use of combination therapy with losartan and lisinopril to that of monotherapy with lisinopril alone.¹⁰⁷ This randomized cross-over trial, produced in the United States, followed 17 participants for 10 weeks to examine the impact of combination ACE-I and AIIRA therapy compared with ACE-I monotherapy on proteinuria and creatinine levels.

Participants in this trial had either glomerulonephritis or diabetic nephropathy; all were proteinuria at baseline (3-4 grams per day on average) and had mildly diminished renal function (baseline glomerular filtration rate of 60-70 ml/min). All included participants had already been on lisinopril 40 mg per day for 3 or more months at the time of enrollment. At randomization, participants remained on lisinopril and were randomized to either losartan 50 mg per day or placebo; all participants were crossed-over to the alternate treatment group after a 2 week washout period. The primary hypothesis of interest was that combination therapy (losartan added to lisinopril) would result in at least a 25% improvement (decrease) in proteinuria compared with monotherapy (lisinopril alone).

This trial reported change in proteinuria from baseline, and found no significant difference in proteinuria in those treated with lisinopril alone (lisinopril plus placebo) compared with those treated with lisinopril and losartan ($P=0.82$). Rough percent change in proteinuria was 14% for those on monotherapy and 4% for those on combination therapy. Change in creatinine clearance was found to not be significant between groups ($P=0.30$), but change in glomerular filtration rate showed a significantly greater decline for those on combination therapy compared with monotherapy ($P=0.017$). No statistically significant differences in blood pressure control were found between groups. One participant was withdrawn from this study. Harms and adverse events were not reported.

Candesartan and ramipril compared with ramipril alone

Two randomized cross-over trials (N=77) addressed the utility of Candesartan and ramipril together compared with ramipril as monotherapy for its impact on proteinuria.^{109, 112} These trials were both produced by the same group of colleagues in Korea, both included proteinuric patients (4 grams per day at baseline) with either IgA nephropathy or diabetic nephropathy. Both received a rating of fair and each trial provided 9-10 months of follow-up. Baseline renal function did differ some between studies, with participants in one group at 30 ml/min baseline creatinine clearance,¹⁰⁹ and the other at approximately 60 ml/min at baseline.¹¹² In one group, all participants were on ramipril 5 mg per day at baseline,¹⁰⁹ and in the other all participants were on ramipril 5-7.5 mg per day at baseline.¹¹² Both trials randomized participants to same dose ramipril with placebo compared with same dose ramipril with candesartan. One trial used candesartan of 4 mg per day,¹⁰⁹ while the other started with candesartan 4 mg per day but then increased to 8 mg per day if tolerated.¹¹² All participants were later crossed over into the alternate treatment arm.

Effectiveness/efficacy outcomes. Both trials examine the change in proteinuria in each treatment group. One trial examined the mean decrease in proteinuria, which was found to be statistically greater in those on combination therapy as compared with those on either ramipril with placebo or ramipril alone ($P<0.05$).¹⁰⁹ Rough percent change in proteinuria was 2% for those on ramipril with placebo compared with -12.5% for those on combination therapy. This study then performed a subgroup analysis by type of chronic kidney disease.¹⁰⁹ These authors noted a statistically significantly greater decline in proteinuria for those IgA nephropathy patients on combination compared with monotherapy ($P<0.05$), but they did not find the same significant decline in proteinuria for combination compared with monotherapy among Diabetic nephropathy patients.¹⁰⁹ The other study examined outcomes exclusively by type of chronic kidney disease; they noted a statistically greater decline in proteinuria for IgA nephropathy patients on combination therapy compared with ramipril alone ($P<0.05$).¹¹² That effect did not hold true for

diabetic nephropathy patients; no statistically different decline in proteinuria on combination compared with monotherapy was noted for this chronic kidney disease subtype. Percent change in proteinuria was -12.3% in IgA on ramipril and candesartan compared with 0.1% in IgA on ramipril with placebo. Percent change in proteinuria was 0.8% in diabetic nephropathy patients on ramipril and candesartan compared with 1.3% in those on ramipril with placebo alone. Both trials reported similar blood pressure control between groups and stable creatinine clearance among all treatment groups. Both trials reported 2 withdrawals.

Harms. One trial reported 2 adverse events (hyperkalemia and hypotension), but did not delineate those events by treatment groups.¹⁰⁹ The other trial reported adverse events based only on candesartan dose (4 mg per day compared with 8 mg per day), but did not compare harms between combination therapy and monotherapy.

Irbesartan and ramipril compared with ramipril alone

One study from Australia examined the use of irbesartan and ramipril together compared with ramipril alone in terms of reduction in proteinuria.¹⁰⁸ This randomized controlled trial enrolled 41 participants for 3 months and received a fair rating. Participants included had a variety of types of chronic kidney disease, including diabetic nephropathy, glomerulonephritis, interstitial nephritis, and those classified as “other.” All participants were proteinuric (baseline ranged from 1.9-9.9 grams per day) with abnormal renal function (baseline creatinine clearance ranged from 57-81 ml/min). All participants were required to have been on ACE-I therapy for 6 months prior to enrollment. After enrollment, all participants given ramipril 5 mg per day; after a 4-12 week compliance period, participants were randomized to receive irbesartan placebo compared with irbesartan in addition to that baseline dose of ramipril. There was also a therapy arm including spironolactone that will not be discussed here.

No significant difference in percent change in proteinuria was found among those on combination therapy compared with ramipril alone ($P=1.0$). Overall percent change in proteinuria was -1.4% and 0.8% for ramipril alone and -15.7% and -11.1% for ramipril with irbesartan at 3 and 6 months respectively. No significant changes in creatinine clearance were noted. Diastolic blood pressure was noted to be higher in the ramipril monotherapy group as compared with the combination therapy group at 6 months ($P=0.046$). A subgroup analysis was performed comparing those with diabetic nephropathy to those with a different type of chronic kidney disease, but no evidence of interaction between treatment effects was found based on nephropathy etiology. One withdrawal was reported.

Adverse events were reported by treatment effect. The 2 reported adverse effects were “feeling unwell or light-headed” and hyperkalemia (potassium level greater than 6 millimoles per liter). One participant on ramipril monotherapy felt light-headed, compared with zero on combination therapy. No participants on ramipril monotherapy or ramipril with irbesartan experienced a potassium level of greater than 6 millimoles per liter.

ACE-I and AIIRA compared with AIIRA alone

Candesartan and benazepril compared with candesartan alone

One trial from Japan compared the use of candesartan with benazepril to monotherapy with candesartan alone to examine the antiproteinuric effects of these therapies.¹¹⁰ This randomized controlled trial followed 86 participants for 36 months (3 years) and was rated fair quality. Types of chronic kidney disease represented among participants included membranoproliferative

glomerulonephritis, focal segmental glomerulosclerosis, membranous nephropathy, and those identified as having “minor glomerular abnormalities.” All participants were proteinuric (1.4 grams per day at baseline) and all had relatively well preserved renal function (baseline creatinine reported as 0.8-0.9 mg/dL). Participants were randomized to receive either candesartan alone (4 to 6 mg per day) or candesartan with benazepril (candesartan 4 mg per day and benazepril 2.5 mg per day). In the candesartan monotherapy group, the candesartan dose was increased to 8 and then 12 mg in 6 month intervals to achieve target blood pressure of less than 125/75 mmHg. In the combination therapy group, benazepril dose was increased to 5 and then 10 mg in the same fashion in order to achieve that same target blood pressure.

This trial reported total reduction in proteinuria; these authors found that the anti-proteinuric effect of combination therapy was statistically greater than that of monotherapy with candesartan alone ($P<0.01$). There was no significant change in glomerular filtration rates between groups, and blood pressure reduction rate was not statistically different between groups. This trial reported 9 withdrawals.

The only reported adverse event was cough, and the incidence of that event (39.1%) was only reported for the combination therapy group. Six of the 9 withdrawals were reportedly related to cough.

Valsartan and benazepril compared with valsartan alone

One trial from Spain examined the use of valsartan with benazepril to valsartan monotherapy for the reduction of proteinuria among proteinuric chronic kidney disease patients.¹¹¹ This randomized controlled trial enrolled 109 participants, provided 5 weeks of follow-up, and was rated as fair quality. Participants had a range of types of chronic kidney disease including IgA nephropathy, glomerulonephritis, nephrosclerosis, and those classified as “other.” All participants had significantly reduced renal function (creatinine clearance of 20-45 ml/min was required), but not all participants were proteinuric (45% to 63% had greater than or equal to 1 gram per day proteinuria). All participants were initially randomized to 1 of 2 doses of valsartan, 80 or 160 mg per day. One week later, all participants on valsartan 80 mg per day and two-thirds of the participants on valsartan 160 mg per day received benazepril 5 or 10 mg per day (based on level of creatinine clearance). The remaining participants on valsartan 160 mg remained on that agent alone as monotherapy.

The primary endpoint was the number of “renal events,” defined as acute renal failure, rapidly progressive renal failure, or hospitalization due to any renal failure event or electrolyte abnormality. No participants in any treatment arm reached this primary endpoint. They also examined changes in proteinuria between treatment groups. Combination therapy was only noted to be statistically superior to monotherapy in terms of reduction in proteinuria with maximal dose combination therapy (valsartan 160 and benazepril 5 or 10 mg per day) compared with monotherapy (valsartan 160 mg per day) ($P=0.047$; 95% CI, -1.044 to -0.01). The lower dose combination therapy (valsartan 80 and benazepril 5 or 10 mg per day) was not statistically superior for reduction in proteinuria compared with monotherapy. Comparison of changes in creatinine clearance was not reported between groups, but creatinine changes were numerically similar in each group. Diastolic blood pressure was not equivalent between groups, and was statistically lower in those on maximum dose combination therapy as compared with valsartan monotherapy ($P=0.00009$). This trial reported 6 withdrawals.

Adverse events were reported by treatment group by percent effected. Total percent of adverse events was numerically greatest among those on monotherapy with valsartan (45%), and

was similar among those on full and half dose combination therapy (25% and 33.3% respectively). Statistical analysis of adverse event rates between groups was not reported, but the event rate of hyperkalemia (potassium greater than 6 millimoles per liter) was highest among those on maximum dose combination therapy (11.9%) compared with similar rates of those on half dose combination or monotherapy (both 4.5%). Additional percent rates for treatment groups can be found in Evidence Table 9, although no statistical comparison is reported.

Diabetic Nephropathy

Summary of findings

Comparison of aliskiren to placebo when added to an AIIRAs or ACE-Is

- When added to losartan
 - Effectiveness/Efficacy: When added to losartan, aliskiren was superior to placebo in reducing urinary albumin-to-creatinine ratio, which appeared independent of change in systolic blood pressure. Analysis of correlation with diastolic blood pressure was not reported. Additionally, a significantly greater proportion of participants achieved a reduction of 50% or more in albuminuria in the aliskiren group. The differences between aliskiren and placebo in deaths, change in estimated glomerular filtration rate or overall withdrawals were not significant, however.
 - Harms: Compared with placebo, no significant increases in risk were found for aliskiren in overall adverse events, any specific adverse events or withdrawals due to adverse events.
 - Subgroups: Greater reductions in albumin-to-creatinine ratio were found regardless of sex, age, or race.

Comparison of AIIRA and ACE-I monotherapies

Effectiveness/efficacy/harms

- Telmisartan compared with enalapril (1 trial, fair quality)
 - With a sample size of 250 participants and a follow-up period of 5 years, the Diabetics Exposed to telmisartan and enalapril (DETAIL) trial is the largest and longest-term trial that compared monotherapy with an AIIRA and an ACE-I in adults with diabetes.
 - Effectiveness/efficacy: Telmisartan was noninferior to enalapril on the primary outcome of change in glomerular filtration rate. Telmisartan and enalapril also had similar effects on other secondary outcomes including all-cause mortality, death due to cardiovascular causes, nonfatal myocardial infarction, congestive heart failure, cerebrovascular accident, kidney failure/required dialysis, increased serum creatinine (greater than 2.3 mg/dL), and overall withdrawals.
 - Harms: No significant differences on incidence of any adverse event or withdrawals due to adverse events.
- Losartan compared with enalapril (5 trials; 4 fair quality, 1 poor quality)
 - Effectiveness/efficacy: There were no deaths, nor any cardiovascular events in a 30-week trial. Consistent findings of no differences in reduction of albumin levels

or change in glomerular filtration rate across 2 trials. Consistent findings of no differences in overall withdrawals across 3 trials. One trial each evaluated change in creatinine, creatinine clearance, and regression of microalbuminuria to normo albuminuria and found no differences between drugs.

- Harms: One, 12-month trial of 103 adults with type 2 diabetes and microalbuminuria found a lower rate of cough with losartan 86 mg compared with enalapril 16 mg, but found no differences between drugs in overall adverse events or withdrawals due to adverse events. Three additional, smaller trials found no differences between drugs in various other drug-related adverse events.
- Losartan compared with quinapril (1 trial, fair quality)
 - Effectiveness/efficacy: Greater reduction in urinary albumin/creatinine ratio for losartan that appeared independent of change in systolic blood pressure, but potential relationship with change in diastolic blood pressure was not addressed. No significant difference in change in serum creatinine.
 - Harms: Significant increase in serum potassium for enalapril, but not losartan.
- Candesartan compared with lisinopril (1 trial, fair quality)
 - Effectiveness/efficacy: No significant difference in mean reduction in urinary albumin/creatinine ratio or in overall withdrawals.
 - Harms: No significant differences in withdrawals due to any adverse event, due to dizziness, feeling weak or both or due to cough.
- Candesartan compared with ramipril (1 trial, fair quality)
 - Effectiveness/efficacy: No significant difference in creatinine, albumin, creatinine clearance, 24-hour urinary protein excretion or overall withdrawals.
 - Harms: No significant difference in overall adverse events, withdrawals due to adverse events, hypotension, hyperkalemia, cough, or “gastrointestinal trouble.”
- Valsartan compared with enalapril (1 trial, fair quality)
 - Effectiveness/efficacy: No significant difference in all-cause mortality, cardiovascular mortality, regression from microalbuminuria to normo albuminuria, progression from microalbuminuria to macroalbuminuria, creatinine, 24-hour urinary albumin, spot urinary albumin/creatinine ratio and overall withdrawal rates.
 - Harms: Incidence of overall adverse events and cough were significantly greater in the enalapril group, but differences in withdrawals due to adverse events were not found.
- Valsartan compared with benazepril (1 trial, fair quality)
 - Effectiveness/efficacy: No significant difference in albuminuria, glomerular filtration rate, creatinine and overall withdrawals.
 - Harms: No significant difference in transient hypotension, anemia, or withdrawals due to adverse events.

Subgroups

- No trials reported subgroup analyses based on demographics, comorbidities, or concomitant medication use.

Combination therapy with AIIRAs and ACE-Is

- Effectiveness/Efficacy

- Overall: No trials reported health outcomes, including all-cause mortality, development of chronic kidney disease, end-stage renal function, need for dialysis or transplantation, hospitalizations, or quality of life
- Losartan plus enalapril (2 trials, both fair quality): Results did not clearly establish that combination therapy had a significantly greater benefit over monotherapy for decrease in urinary protein excretion that was independent from blood pressure control, regression from microalbuminuria to normo albuminuria, creatinine clearance, or overall withdrawals.
- Combination therapy with candesartan plus an ACE-I (2 trials)
 - Candesartan plus lisinopril (Fair quality): A superior decrease in albumin-to-creatinine ratio was found for combination therapy when compared with candesartan monotherapy (mean difference, -34%; 95% CI, -3 to -55), but not when compared with lisinopril monotherapy (mean difference, -18%; 95% CI, -20 to +44). However, independence from superior overall blood-pressure control was not established.
 - Candesartan plus ramipril (Fair quality): Decrease in urinary protein excretion was significantly greater for combination therapy (-29%) compared with candesartan monotherapy (-19%) and ramipril monotherapy (-15%), but independence from superior overall blood pressure control was not established. No advantage for combination therapy in albumin, serum creatinine or creatinine clearance.
- Combination therapy with irbesartan plus enalapril (1 trial, good quality): Irbesartan plus enalapril: Lowering of albuminuria was 25% greater with combination compared with enalapril monotherapy, but independence from overall blood-pressure control was not established. No advantage for combination therapy in glomerular filtration rate or creatinine.
- Combination therapy with valsartan plus benazepril (1 trial, fair quality): Combination therapy resulted in an additional reduction of albuminuria (mg/24 hours) compared with valsartan monotherapy (-39%; 95% CI, -23 to -51) and compared with benazepril monotherapy (-37%; 95% CI, -22 to -49), which was found to be independent of change in arterial blood pressure for the comparison of combination to benazepril monotherapy. No significant advantage was found for combination therapy in effects on creatinine, but there was noted to be a significantly greater reversible reduction in glomerular filtration rate during the 8-week study period.
- Harms: No trial reported that combination therapy resulted in significantly greater incidence of overall adverse events, any specific adverse events, or withdrawals due to adverse events.
- Subgroups: No trial reported subgroup analyses based on demographics, comorbidities, or concomitant medications.

Detailed assessment

Aliskiren used in combination with an AIIRA or an ACE-I

We included 1, fair-quality, multicenter, international trial, the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial, that compared treatment with aliskiren (150 mg for 3

months, then increased to 300 mg for another 3 months) or placebo, in addition to losartan 100 mg in 599 adults with type 2 diabetes and macroalbuminuria.¹¹⁸

Effectiveness/efficacy

The primary efficacy measure was the percentage reduction in the early-morning urinary albumin-to-creatinine ratio, which was 20% greater for aliskiren compared with placebo (95% CI, 11 to 29). The greater reduction in urinary albumin-to-creatinine ratio for aliskiren decreased slightly, but remained significant after adjustment for change in systolic blood pressure (18%; 95% CI, 5 to 30). Results following adjustment for change in diastolic blood pressure were not reported. As for secondary outcomes, a significantly greater proportion of participants in the aliskiren group achieved a reduction of 50% or more in albuminuria (25% compared with 12%, $P<0.001$), but the difference between aliskiren and placebo was not statistically significant for mean rate of decline in estimated glomerular filtration rate (-2.4 compared with -3.8 ml/min/1.73 m²; $P=0.07$) Only 2 deaths occurred during the trial, both within the placebo group (0.7%). Incidence of overall withdrawals was similar for aliskiren (14%) compared with placebo (11%).

Harms

In both treatment groups, incidence of overall adverse events was 67% and 6% of participants withdrew due to adverse events. There were no significant differences between aliskiren and placebo in incidence of hypotension (4% compared with 1%), hyperkalemia (5% compared with 6%), cough (2% in both groups), peripheral edema (4% compared with 8%), diarrhea (3% in both groups), or any other specific adverse events.

Subgroups

In subgroup analysis, greater reductions in the albumin-to-creatinine ratio were found regardless of sex, race (White or non-White), or age (below median or at or above median).

Comparison of AIIRA and ACE-I monotherapies in adults with diabetic nephropathy

We included 16 trials^{119-132, 133l, 134, 135} and 1 good-quality Cochrane review¹³⁶ that compared monotherapy with an AIIRA to monotherapy with an ACE-I. Losartan was compared with enalapril in 5 trials^{119, 123, 128, 133, 135} and to quinapril in 1 trial.¹²⁹ Telmisartan was compared with enalapril in the Diabetics Exposed to Telmisartan and enalapril (DETAIL) trial.¹²⁰⁻¹²² Candesartan was compared with lisinopril in 1 trial¹³¹ and to ramipril in 1 trial.¹³² Irbesartan was compared with perindopril in 1 trial.¹³⁰ Valsartan was compared with benazepril in 1 trial,¹²⁵ to enalapril in 1 trial,¹²⁷ and to captopril in 1 trial.¹³⁴ Data abstraction and quality assessment can be found in Evidence Tables 20 and 21, respectively. Only 1 trial was rated good quality,¹²⁶ 12 were rated fair quality,^{118, 119, 122, 124, 125, 127-129, 131-133, 135} and 3 were rated poor quality.^{123, 130, 134} We found no trials involving comparisons of either eprosartan or olmesartan to an ACE-I and no trials involving comparisons of cilazapril, moexipril or trandolapril to an AIIRA.

Telmisartan

Telmisartan compared with enalapril

With a sample size of 250 participants and a follow-up period of 5 years, the Diabetics Exposed to Telmisartan and enalapril (DETAIL) trial is the largest and longest-term trial that compared monotherapy with an AIIRA and an ACE-I in adults with diabetes.¹²⁰⁻¹²² We rated DETAIL as fair quality due to their exclusion of 14% of patients from the analysis of their primary outcome. The DETAIL trial enrolled adults with type 2 diabetes, mild to moderate hypertension, normal renal function, and either microalbuminuria (82%) or macroalbuminuria (18%) from across 39 center in northern Europe. Use of concomitant antihypertensive drugs during the trial was allowed after 2 months if resting systolic blood pressure was above 160 mm Hg or if resting diastolic blood pressure was above 100 mm Hg and these included diuretics in 52% of participants, beta blockers in 39%, calcium channel blockers in 46% and “other”, unspecified antihypertensive agents in 35%.

Effectiveness/efficacy outcomes. DETAIL was a noninferiority trial designed to evaluate the hypothesis that telmisartan was not worse than enalapril on the primary outcome of change in glomerular filtration rate by more than the predefined margin of 10.0 ml/min/1.73 m². After 5 years, mean change in glomerular filtration rate was -17.9 mg/min/1.73 m² for telmisartan and -14.9 mg/min/1.73 m² for enalapril. This resulted in a treatment difference of -3 mg/min/1.73 m², with a lower bound of the 95% CI (-7.6, in favor of enalapril) that indicated that telmisartan was not inferior. Serum creatinine increased by 10% in both treatment groups. Similar results were found for telmisartan and enalapril on other secondary outcomes including all-cause mortality (5.0% compared with 4.6%), death due to cardiovascular causes (2.5% compared with 1.5%), nonfatal myocardial infarction (7.5% compared with 4.6%), congestive heart failure (7.5% compared with 5.4%), cerebrovascular accident (5.0% compared with 4.6%), kidney failure/required dialysis (0% compared with 0%), raised serum creatinine to less than 2.3 mg/dL (0% compared with 0%), or overall withdrawals (32% compared with 34%). The Cochrane review reported a risk ratio of 0.92 (95% CI, 0.31 to 2.78) for all-cause mortality and 0.62 (95% CI, 0.10 to 3.62) for cardiovascular mortality for the comparison of enalapril to telmisartan.¹³⁶

Harms. Incidence of any adverse event (96% compared with 100%) and withdrawals due to adverse events (17% compared with 23%) were similar for telmisartan and enalapril. No other adverse events were reported.

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Losartan

Losartan compared with enalapril

Losartan was compared with enalapril in 5 trials (N=201) conducted in Canada,¹²⁸ Demark,¹¹⁹ and Turkey.^{123, 133, 135} Four were rated fair quality and the other was rated poor quality and its results will not be discussed here.¹²³ Losartan dosage ranged from 50 mg to 100 mg. Enalapril dosage ranged from 5 mg to 20 mg. Trials were heterogenous in terms of duration, participant characteristics, and outcome reporting. Follow-up duration ranged from 2 months¹¹⁹ to 1 year in 2 trials.^{128, 133} One trial enrolled adults with type 1 diabetes.¹¹⁹ Three trials enrolled adults with type 2 diabetes.^{128, 133, 135} Diabetes type was unspecified in the fifth trial.¹²³ Three trials enrolled

adults with microalbuminuria^{128, 133, 135} and 2 trials enrolled adults with macroalbuminuria.^{119, 123} Renal function was normal in 2 trials,^{119, 135} abnormal in trial,¹²³ and not clearly described in the remaining 2 trials.^{128, 133}

Effectiveness/efficacy outcomes. One trial of 26 adults with type 2 diabetes, microalbuminuria, and mild-to-moderate hypertension from a single center in Turkey reported that there were no deaths nor any cardiovascular events during the course of the 30-week trial.¹³⁵

Another trial (N=34), conducted at a single center in Turkey, reported the numbers of participants that regressed from microalbuminuria to normo albuminuria over 12 months of follow-up.¹³³ In the enalapril 5 mg group, 10 of 12 participants (83%) regressed to normo albuminuria, compared with 8 of 12 in the losartan 50 mg group (67%). The difference between groups was not statistically significant, likely due to the small sample size. Based on results of a supplemental analysis reported by the Cochrane review, the risk ratio (random effects model) for the comparison of enalapril to losartan was 1.22 (95% CI, 0.76 to 1.94).¹³⁶

Two trials reported change in urinary albumin excretion and neither found a statistically significant difference between losartan and enalapril.^{119, 135} After 2 months, in 16 type 1 diabetics with macroalbuminuria, geometric mean urinary albumin was reduced from a baseline value of 1156 (95% CI, 643 to 2080) mg/24 hours by 33% (12% to 51%) to 775 (445-1349) mg/24 hours for losartan 50 mg, by 44% (26% to 57%) to 651 (377-1126) mg/24 hours for losartan 100 mg, by 45% (23% to 61%) to 631 (340-1173) mg/24 hours for enalapril 10 mg and by 59% (39% to 72%) to 477 (251-910) mg/24 hours for enalapril 20 mg.¹¹⁹ After 6 months in 26 type 2 diabetics with microalbuminuria, albumin excretion rate decreased from 80.1 mg/day at baseline by 76% for losartan 50-100 mg and decreased from 83.5 mg/day at baseline by 79% for enalapril 5-20 mg.¹³⁵

Change in creatinine clearance was reported in the 30-week trial of 26 type 2 diabetics with normal renal function.¹³⁵ In the losartan group, there was a slight decrease in creatinine clearance (-4% from 115.9 ml/min at baseline), whereas for enalapril there was a slight increase (+10% from 102.6 mg/min). However, the difference between groups was not significant. Change in serum creatinine was reported by 1 crossover trial of 16 type 1 diabetics with normal renal function after 2 months each of losartan 50 mg, losartan 100 mg, enalapril 10 mg, and enalapril 20 mg.¹¹⁹ Compared with placebo (1.08 ± 0.06 mg/dL), changes in serum creatinine were similarly slight for losartan 50 mg (1.06 ± 0.06 mg/dL), losartan 100 mg (1.04 ± 0.08), enalapril 10 mg (1.08 ± 0.06), and enalapril 20 mg (1.01 ± 0.07). In this same trial, there were also no significant differences in glomerular filtration rate at endpoint (ml/min/1.73 m²) between losartan 50 mg (91 ± 6), losartan 100 mg (92 ± 7), enalapril 10 mg (96 ± 5) and enalapril 20 mg (87 ± 6). In another trial of 103 type 2 diabetics with normal baseline renal function, geometric mean glomerular filtration rate (mL/min) was 96.7 in the losartan 86.3 mg group and 95.3 in the enalapril 16 mg group at baseline and declined by 9% in both groups after 1 year of treatment.¹²⁸ Decline in glomerular filtration rate was significantly positively correlated with decline in 24-hour mean systolic and diastolic ambulatory blood pressure during the first 12 weeks of treatment, but the correlation was no longer significant at 1 year.¹²⁸

Overall withdrawals were reported in 3 trials that compared losartan to enalapril and no significant differences between the drugs were found.^{119, 128, 135} In 1 crossover trial, all 16 participants completed all 5 treatment periods consisting of 2 months each of placebo, losartan 50 mg, losartan 100 mg, enalapril 10 mg and enalapril 20 mg.¹¹⁹ In the other trials, withdrawal

rates for losartan and enalapril, respectively were 11.5% and 9.8% after 12 months¹²⁸ and 8% in both groups after 30 weeks.¹³⁵

Harms. Information on harms was reported in 4 trials.^{119, 128, 133, 135} The only statistically significant difference between the drugs noted was for incidence of cough in 1 trial.¹²⁸ Only 1 of the 3 trials reported results of statistical analyses that compared losartan to enalapril on a select number of events.¹²⁸ In this trial, losartan 86 mg was compared with enalapril 16 mg in 103 adults with type 2 diabetes and microalbuminuria and, after 12 months, there was a significantly lower rate of cough in the losartan group (0% compared with 14%, $P=0.006$), but there were no significant differences in rates of overall adverse events (data not reported) or withdrawals due to adverse events (3.8% compared with 2.0%). Only 1 participant from the enalapril group (8%) withdrew due to adverse events (i.e., cough and dizziness) over the 30-week trial.¹³⁵ Otherwise, in the 2-month, crossover trial of type 1 diabetics with macroalbuminuria that compared losartan 50 mg and 100 mg with enalapril 10 mg and 20 mg the only information provided about harms was that, “no patients reported side effects that could be related to the study medication.”¹¹⁹ And, in the 12-month trial of 34 adults with type 2 diabetes and microalbuminuria, the only information provided about harms was that, “none of the subjects experienced any drug related adverse events including cough, hypoglycemia, hypotension, dizziness, fatigue or malaise.”¹³³

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Losartan compared with quinapril

Losartan 50 mg was compared with quinapril 20 mg in a fair-quality, crossover, single-blind, 4-week trial of 41 adults with type 2 diabetes, macroalbuminuria and normal renal function from a single, secondary care institution in Singapore.¹²⁹ Other antihypertensive agents including hydrochlorothiazide, calcium channel blockers and beta blockers were used concomitantly by 27% of participants during the trial.

Effectiveness/efficacy. The only eligible effectiveness/efficacy outcomes reported in this trial were reduction in urinary albumin/creatinine ratio and change in serum creatinine. Mean reduction in urinary albumin/creatinine ratio (mg/g) was significantly greater for losartan (−93) compared with quinapril (−49; $P=0.025$). Results of a linear regression analysis suggested that the greater reduction in urinary albumin/creatinine ratio was independent of any difference in systolic blood pressure ($P=0.15$). But, the potential relationship between changes in albuminuria and diastolic blood pressure were not addressed. Serum creatinine increased from 0.86 mg/dL to 0.87 mg/dL in both groups. All patients completed the trial.

Harms. Reporting of harms was limited to change in serum potassium, which increased from 4.3 mM to 4.4 mM (P value not reported) for losartan and from 4.2 mM to 4.4 mM ($P=0.01$) for enalapril.

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Candesartan

Candesartan compared with lisinopril

Candesartan 16 mg (N=66) was compared with lisinopril 20 mg (N=64) in the fair-quality, 24-week Candesartan and Lisinopril Microalbuminuria (CALM) trial that enrolled adults with type 2 diabetes, microalbuminuria, and normal renal function across multiple centers in Australia, Denmark, Finland, and Israel.¹²⁹ Hydrochlorothiazide 12.5 mg once daily was used concomitantly by 10.6% of participants in the candesartan group and by 9.4% in the lisinopril group.

Effectiveness/efficacy. No significant differences were found in the only eligible effectiveness/efficacy outcomes reported in this trial, which were the mean percent reduction in urinary albumin/creatinine ratio, adjusted for center, treatment, baseline value, weight, and diastolic blood pressure change and overall withdrawals. Mean reduction was -24% (95% CI, 0 to -43; $P=0.05$) for candesartan and -39% (-20% to -54%; $P<0.001$). Overall withdrawal rates were similar for candesartan and lisinopril (26% compared with 28%).

Harms. Reporting of harms was sparse, and there were no significant differences between candesartan and lisinopril in withdrawals due to any adverse event (3% compared with 8%), withdrawals due to dizziness, feeling weak or both (3% in both groups), or in withdrawals due to cough (0% compared with 5%).

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Candesartan compared with ramipril

Candesartan 16 mg was compared with ramipril 10 mg in a fair-quality, 16-week crossover trial of 21 adults (mean age of 49 years, 52% male) with type 2 diabetes, macroalbuminuria and abnormal renal function enrolled from a single center in Korea.¹³² The percent of participants for whom use of other concomitant antihypertensive drugs was necessary to achieve the blood pressure goal of below 140/80 mmHg was 57% for calcium channel blockers, 43% for diuretics, 28% for beta blockers, and 19% for alpha antagonists.

Effectiveness/efficacy. At baseline, mean values were 1.8 mg/dL for creatinine, 3.0 g/dL for albumin, 40.6 ml/min/1.73 m² for creatinine clearance, and 4.1 g/24 hours for 24-hour urinary protein excretion. There were no significant differences between candesartan and ramipril treatment periods for creatinine (1.9 mg/dL in both groups), albumin (3.1 g/dL compared with 3.0 g/dL), creatinine clearance (39.0 compared with 40.7 ml/min/1.73 m²), or 24-hour urinary protein excretion (3.3 compared with 3.5 g/24 hours). Overall withdrawals were not reported for each group separately. No other eligible effectiveness/efficacy outcomes were reported.

Harms. For harms, there were no significant differences between candesartan and ramipril in overall adverse events (19% compared with 14%), withdrawals due to adverse events (5% in both groups), hypotension (5% compared with 0), hyperkalemia, defined as greater than 6.0 mEq/l (0 compared with 5%), cough (0 compared with 5%), and gastrointestinal trouble (0 compared with 0).

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Valsartan

Valsartan compared with enalapril

Valsartan 109 mg was compared with enalapril 6.3 mg in a fair-quality, 1-year parallel trial of 42 adults (mean age of 61 years, 40% male, 100% Chinese) with type 2 diabetes, microalbuminuria and normal renal function enrolled from a single center in China.¹²⁷ Method of blinding was not clearly described. At the time of enrollment, all patients had hypertension and were already taking antihypertensive drugs other than AIIRAs or ACE-Is. Whether or not they were allowed to continue prior antihypertensive treatment was not clearly described. Dose titration of valsartan and enalapril was based on reaching a target blood pressure of below 140/90 mm Hg.

Effectiveness/efficacy. At baseline, mean values were 0.95 mg/dL for creatinine, 70.4 mg/d for 24 hour urinary albumin and 5.1 mg/mmol for spot urinary albumin/creatinine ratio. At the end of the trial, similar changes were found for valsartan and enalapril on creatinine (−3.4% compared with +55.5%; $P=0.190$), 24-hour urinary albumin (−6% compared with −5%; $P=0.906$) and on spot urinary albumin/creatinine ratio (−8% compared with +34%; $P=0.453$). Overall, regression of albuminuria was observed in 2 (9.5%) participants in the valsartan group and 2 (10%) participants in the enalapril group. Although unavailable from the original trial publication,¹²⁷ the Cochrane review¹³⁶ reported results of supplemental risk ratio analyses for the comparison of valsartan to enalapril on incidence of all-cause mortality, cardiovascular mortality, regression from microalbuminuria to normo albuminuria, and progression from microalbuminuria to macroalbuminuria. The Cochrane review reported that there were no cases of all-cause mortality or cardiovascular mortality in either treatment group and, for the losartan group, there was a slightly lower chance of regressing from microalbuminuria to normo albuminuria (0% compared with 5%; relative risk, 0.35; 95% CI, 0.02 to 8.10) and a slightly higher risk of progressing from microalbuminuria to macroalbuminuria (5% compared with 0%; relative risk, 3.14; 95% CI, 0.14 to 72.92). Overall withdrawals were similar for valsartan (5%) compared with enalapril (0%).

Harms. Significantly more participants in the enalapril group reported any adverse event (45% compared with 14%; $P=0.015$) and cough (35% compared with 0; $P=0.003$), but no patients in either group withdrew due to adverse events. The Cochrane review reported a risk ratio for cough of 0.06 (95% CI, 0.00 to 1.05) for the comparison of valsartan to enalapril.¹³⁶

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Valsartan compared with benazepril

Valsartan 80 mg was compared with benazepril 20 mg in a fair-quality, crossover trial of 20 adults (mean age of 43 years, 72% male) with type 1 diabetes (mean duration of 30 years) and macroalbuminuria enrolled from a single center in Denmark.¹²⁵ Treatment periods included placebo, monotherapy with valsartan and benazepril, and their combination and each lasted 8 weeks in duration. All previous antihypertensive medication, except loop diuretics, was

withdrawn at the screening visit. Median dose of concomitant furosemide was 40 mg (range 20 mg to 250 mg).

Effectiveness/efficacy. Placebo value was 701 mg/24 hours for albuminuria, 82 ml/min/1.73 m² for glomerular filtration rate, and 1.30 mg/dL for creatinine. Declines from placebo were similar for valsartan and benazepril for albuminuria (65 for both drugs), glomerular filtration rate (4 compared with 3), and creatinine (0.02 compared with -0.01). Overall withdrawals were similar for valsartan (0%) compared with benazepril (11%).

Harms. Incidence of any adverse event was not reported. Transient hypotension (0% compared with 11%), treatment for anemia (0% in both groups) and withdrawals due to adverse events (0% compared with 11%) were similar for valsartan and benazepril.

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Irbesartan

Irbesartan compared with perindopril

Irbesartan 300 mg was compared with perindopril 8 mg in an open-label crossover trial of 20 adults (mean age of 54 years, 25% male, 50% nonwhite) with type 2 diabetes, hypertension, macroalbuminuria, and abnormal renal function enrolled from a single center in Brazil.¹³⁰ This trial was rated poor quality. Thus, a detailed analysis of its findings will not be provided. Reasons for the poor quality rating include the lack of use of blinding, an overall high withdrawal rate (25%), and a lack of sufficient detail for properly assessing the adequacy of randomization and allocation concealment methods or whether or not an intention-to-treat analysis was performed.

Comparison of combination therapy with an AIIRA plus an ACE-I to monotherapy with an AIIRA and/or an ACE-I

We included 8 trials that compared the combination of an AIIRA and an ACE-I with either or both as monotherapy.^{123-126, 130-133} We also found a publication on the design and methods of the ongoing Veteran's Affairs NEPHROpathy in Diabetes Study (VA NEPHRON-D) that compares the combination of losartan and lisinopril to monotherapy with losartan in adults with type 2 diabetes with overt nephropathy and a glomerular filtration rate between 30 and 89.9 ml/min/1.73 m².¹³⁷ Results were not yet available at the time of this report, but when published, will be considered for inclusion in a future update.

The majority of trials were rated fair quality^{124, 125, 131-133} However, 1 trial was rated good quality¹²⁶ and 2 trials were rated poor quality.^{123, 130} Results from the poor quality trials will not be discussed in this detailed analysis but they can be found in Evidence Table 21.¹²³ In 1 poor-quality trial, participants were originally randomized to 12 weeks of monotherapy with either losartan 50 mg (n=11) or enalapril 10 mg (n=11). Then, 45% of participants from each monotherapy group were given the combination of losartan 50 mg plus enalapril 10 mg for an additional 12 weeks. No details were provided about the method of selecting which participants were given the combination therapy and whether or not there were any significant differences in important clinical characteristics between the subset of participants in the combination therapy

group compared with the overall sample. Reasons for the poor quality rating of the other trial include the lack of use of blinding, an overall high withdrawal rate (25%), and a lack of sufficient detail for properly assessing the adequacy of randomization and allocation concealment methods or whether or not an intention-to-treat analysis was performed.¹³⁰

The majority of trials ranged from 8 weeks to 16 weeks in duration.^{124-126, 130, 132} A few trials were longer-term in duration, with 24 weeks¹³¹ and 1 year of follow-up.¹³³ All but 1 trial (N=197)¹³¹ had small sample sizes, ranging from 20 to 34 participants. Among the trials, 2 enrolled adults with type 1 diabetes and macroalbuminuria,^{125, 126} and 5 enrolled adults with type 2 diabetes and either microalbuminuria^{131, 133} or macroalbuminuria.^{124, 130, 132}

Two trials compared the combination of losartan plus enalapril to monotherapy with either enalapril^{124, 133} or losartan.¹³³ Two trials compared combination therapy with irbesartan plus either enalapril¹²⁶ or perindopril¹³⁰ to monotherapy with the corresponding individual AIIRAs and ACE-Is. Two trials compared combination therapy with candesartan plus either lisinopril¹³¹ or ramipril¹³² to monotherapy with the corresponding individual AIIRAs and ACE-Is. One trial compared combination therapy with valsartan plus benazepril to monotherapy with valsartan and benazepril.¹²⁵

Only 1 trial reported regression from microalbuminuria to normo albuminuria after 12 months and involved the comparison of combination therapy with losartan 50 mg plus enalapril 5 mg to monotherapy with either losartan 50 mg or enalapril 5 mg in type 2 diabetics with microalbuminuria.¹³³ Otherwise, no other trials reported health outcomes, including all-cause mortality, development of chronic kidney disease, end-stage renal function, need for dialysis or transplantation, hospitalizations, or quality of life. Renal function outcome reporting was heterogeneous across trials. Changes in glomerular filtration rate was reported in 3 trials,^{125, 126, 130} in albuminuria in 3 trials,^{125, 126, 132} in proteinuria in 3 trials,^{124, 130, 132} in albumin:creatinine ratio in 1 trial,¹³¹ in creatinine in 4 trials,^{125, 126, 130, 132} and in creatinine clearance in 2 trials.^{124, 132}

Overall, combination therapy was found to have statistically significant antiproteinuric effects compared with monotherapies in 5^{124-126, 131, 132} of 7 trials. But, in only 1 of the 5 trials, was the antiproteinuric benefit of combination therapy distinguished as being independent of the overall blood-pressure control.¹²⁵ No significant differences between combination therapy and monotherapy with either an AIIRA or an ACE-I were reported in overall withdrawals, withdrawals due to adverse events or in incidence of adverse events.

Combination therapy with losartan plus enalapril

Two trials compared the combination of losartan plus enalapril to monotherapy with either enalapril^{124, 133} or losartan.¹³³ In 1 trial, all participants were given enalapril 5 mg for 12 weeks, then were randomized to doubling of the enalapril dosage to 10 mg (n=13) or to combination therapy with losartan 50 mg plus enalapril 5 mg (n=13) for another 12 weeks.¹²⁴

Effectiveness/efficacy. In the combination therapy group, urinary protein excretion decreased from 1.28 grams/day to 0.70 grams/day. This was described as a significantly greater level of reduction ($P<0.05$) than in the doubled enalapril group, but the data were not reported. Any attempt to evaluate the potential confounding effects of blood pressure control on urinary protein excretion was not reported, however. Combination therapy did not offer a significant benefit over monotherapy in change in creatinine clearance. All participants completed the trial. In the other trial (N=34), participants were randomly assigned to 12 months of treatment with either monotherapy of either losartan 50 mg or enalapril 5 mg, or their combination. Combination

therapy did not offer a superior benefit over either monotherapy with losartan or enalapril in regression from microalbuminuria to normo albuminuria (70% compared with 67% or 83%). Attrition was not reported.

Harms. Information on harms was only reported in 1 of the 2 trials, which indicated that no participants experienced any drug-related adverse events, including cough, hypoglycemia, hypotension, dizziness, fatigue, or malaise.¹³³

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Combination therapy with candesartan plus an ACE-I

Candesartan plus lisinopril

The Candesartan and Lisinopril Microalbuminuria (CALM) trial randomized 197 participants to 4 treatment groups: (1) 24 weeks of monotherapy with candesartan 16 mg, n=66; (2) 24 weeks of monotherapy with lisinopril 20 mg, n=64; (3) 12 weeks of candesartan 16 mg monotherapy, followed by 12 weeks of combination therapy with candesartan 16 mg plus lisinopril 20 mg, n=34; and (4) 12 weeks of monotherapy with lisinopril 20 mg, followed by 12 weeks of combination therapy with candesartan 16 mg plus lisinopril 20 mg, n=35.¹³¹ For the outcome analysis, participants from groups 3 and 4 were combined and compared with participants from groups 1 and 2.

Effectiveness/efficacy. At baseline, albumin:creatinine ratio (mg/mmol) was 5.6 for combination therapy, 7.2 for candesartan monotherapy, and 5.9 for lisinopril monotherapy. Change in albumin:creatinine ratio after 24 weeks was -50% (95% CI, -36 to -61) for combination therapy, -24% for candesartan monotherapy (95% CI, 0 to -43), and -39% for lisinopril monotherapy (95% CI, -20 to -54). After adjustment for center, treatment, baseline value, weight and change in diastolic blood pressure, the mean difference between combination and candesartan was -34% (95% CI, -3 to -55) and between combination and lisinopril was -18% (95% CI, -20 to +44). Overall rates of withdrawal were similar for combination therapy (27%) compared with candesartan (26%) and lisinopril (28%).

Harms. Rates of overall adverse events were not reported. A slight increase of potassium was observed only in the combination therapy group, at the level of +0.30 mmol/l. Withdrawals due to adverse events were similar for combination therapy (1.5%) compared with candesartan monotherapy (3%) and lisinopril monotherapy (7.8%).

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Candesartan plus ramipril

One trial randomized 21 adults with type 2 diabetes, macroalbuminuria, and abnormal renal function from a single center in Korea to 16 weeks of treatment with either low-dose combination therapy with candesartan 8 mg plus ramipril 5 mg, or twofold higher dosages of either monotherapy with candesartan 16 mg or ramipril 10 mg.¹³²

Effectiveness/efficacy. At baseline 24-hour urinary protein excretion (grams/24 hours) was 4.1 overall. At the end of treatment, the greatest reduction was found for the combination therapy group (29%; $P < 0.05$), compared with either monotherapy with candesartan (19%) or with ramipril (15%). The potential confounding effects of blood pressure control on urinary protein excretion were not reported, however. Changes in albumin, serum creatinine, or creatinine clearance were not significantly different for low-dose combination therapy compared with monotherapy with either candesartan or ramipril. A total of 16% of participants did not complete the trial. Individual treatment group withdrawal rates were not provided separately.

Harms. There were no significant differences between the combination therapy, candesartan monotherapy, and ramipril monotherapy groups in overall adverse events (19% compared with 19% and 14%, respectively), hypotension (9.5% compared with 4.8% and 0%), hyperkalemia, defined as 6.0 mEq/l (9.5% compared with 0% and 4.8%), cough (0% compared with 0% and 4.8%), gastrointestinal trouble (0% in each group), or in withdrawals due to adverse events (5% compared with 5% and 0%).

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Combination therapy with irbesartan plus enalapril

One trial compared the effects of combination therapy with irbesartan plus enalapril to monotherapy with enalapril on albuminuria, glomerular filtration rate and creatinine in 23 adults with type 1 diabetes and macroalbuminuria.¹²⁶ All participants received enalapril 40 mg daily for 3 months and then were randomized to the addition of irbesartan 300 mg or placebo for 8 weeks.

Effectiveness/efficacy. Compared with enalapril monotherapy (519 mg/24 hours), albuminuria was 25% lower (95% CI, -34 to -15; $P < 0.001$) with combination therapy (373 mg/24 hours). But, authors commented that they were not able to ascertain whether the superior reduction in albuminuria for combination therapy was independent of its superior blood-pressure lowering action. Participants' renal function was normal at baseline and differences between combination therapy and enalapril monotherapy in effects on glomerular filtration rate and creatinine were not found. All participants completed the trial.

Harms. There were no significant differences between combination therapy and monotherapy in incidence of transient hypotension (17% compared with 0%), increase in plasma potassium to > 5.2 mmol/L (4% compared with 4%), or need for treatment for anemia (0% in both groups).

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Combination therapy with valsartan plus benazepril

One crossover trial randomized 20 adults with type 1 diabetes and macroalbuminuria to 8 weeks each of valsartan 80 mg, benazepril 20 mg, their combination, and placebo.¹²⁵ Median albuminuria at baseline was 362 mg/24 hours (range, 80 to 2628).

Effectiveness/efficacy. Compared with monotherapy with either valsartan (225 mg/24 hours) or benazepril (239 mg/24 hours), mean albuminuria was significantly lower after combination therapy (138 mg/24 hours). The additional reduction in albuminuria with combination therapy was -39% (95% CI, -23 to -51) compared with valsartan and -37% (95% CI, -22 to -49) compared with benazepril. Based on results from a linear regression analysis, however, when compared with valsartan monotherapy, the additional reduction in albuminuria with combination therapy was significantly correlated with an additional reduction in mean arterial blood pressure ($R=0.65$; $P=0.01$). In contrast, when compared with benazepril monotherapy, the additional reduction in albuminuria appeared independent of an additional reduction in albuminuria ($R=0.11$; $P=0.66$). The small sample size and the relatively brief treatment duration limit the strength of this finding, however.

Reversible reduction in glomerular filtration rate ($\text{ml}/\text{min}/1.73 \text{ m}^2$) was significantly greater with combination therapy compared with valsartan monotherapy (-6; 95% CI, -2 to -11) and compared with benazepril monotherapy (-7; 95% CI, -3 to -11). No advantage was found for combination over either monotherapy in change in creatinine. Only 2 participants withdrew from the trial (11%), both due to adverse events and both during benazepril monotherapy.

Harms. Incidence of overall adverse events was not reported. Transient hypotension occurred in 33% of participants during combination therapy, 0% during valsartan monotherapy and 11% during benazepril monotherapy, but the differences were not significant due to the small sample size.

Subgroups. Results of subgroup analyses based on demographics, comorbidities or concomitant medication use were not reported.

Serious Harms in Observational Studies: All Populations

Summary of findings

- Fourteen observational studies with sample size greater than 1000 subjects examined adverse events in ACE-I or AIIRAs.
- The follow-up period ranged between 6 weeks and 12 months.
- Most studies were in hypertensive populations.
- A number of large post-marketing studies were identified which likely present data representative of broad, primary care populations.
- Rates of total withdrawals from studies range between 3.3% and 19.7%.
- Rates of withdrawals due to adverse events were generally less than 5% (range 1.4% to 9.0%) and were generally due to nonserious events.
- Rates of specific adverse events were as follows:
 - Angioedema: 0.02 to 0.06%; similar rates in ACE-I and AIIRAs (total 4 studies)
 - Hypotension (either postural or not defined) was reported at a rate of about 0.3% in several studies of ACE-I; rates were not reported in studies of AIIRAs.
 - Serious renal adverse events were rare with ACE-I: hyperkalemia was noted in 0.13% with enalapril, a significant rise in serum creatinine in 0.2% with lisinopril, and renal dysfunction at <0.2% with perindopril.¹³⁸

- Only 1 study reported on the renal effects of AIIRAs: rates of dialysis were low with losartan.
- Death and cardiovascular disease events were reported in several studies, but only 1 study compared rates (with captopril) to those in general populations: death rates were 80% of the expected rate and cardiovascular deaths were 4% more than expected.
- Rates of breast cancer were not elevated in a single case-control study of captopril, enalapril, and lisinopril.
- Large observational studies reported few data on adverse events in age and sex subgroups and no data on subgroups based on race/ethnicity or the presence of comorbid conditions.
 - Captopril-related adverse events were more frequently in women over 70 years of age in 1 study.
 - Withdrawals due to renal insufficiency increased with age in 1 study of perindopril.
 - In a meta-analysis of telmisartan studies, the incidence of all-cause adverse events per person-year was lower in persons > 65 years of age than in younger persons, but serious adverse events occurred at a higher rate in the older age group.

Detailed assessment

We identified 14 studies with sample size ≥ 1000 patients that examined adverse events in either ACE-I¹³⁸⁻¹⁴⁵ or AIIRAs.¹⁴⁶⁻¹⁵¹ No studies examined aliskiren. Most studies were open-label, prospective, single-group cohort studies^{139, 140, 142-144, 146, 147, 149} or post-marketing surveillance studies,^{138, 148, 150} while several were retrospective.^{145, 151} One study was a case-control study of breast cancer.¹⁴¹ Among the cohort studies, sample size ranged between 2096¹⁴⁴ and over 67 000.¹³⁹ Median follow-up period ranged between 6 weeks¹⁴⁹ and 12 months.¹³⁸ One study examined data from randomized controlled trials, comparing treatment arms across trials (i.e., observational design).¹⁵¹ Most studies examined populations with hypertension, with 1 study of heart failure¹⁴³ and 2 with varied diagnoses.^{145, 148}

Representatives of the study populations likely varied across studies, although the large sample sizes and broad recruitment strategies suggest that the data we reviewed are likely applicable to broad populations. Study recruitment encompassed most or all of the target population of interest in several large, post-marketing studies of all patients taking the study drug within the participating physicians' practices, including several in the United Kingdom^{139, 146, 148} and in Germany.^{149, 150} Thorp and coauthors¹⁴⁵ examined population-based data within a health maintenance organization. Gonzalez-Perez and colleagues¹⁴¹ examined patients in the United Kingdom National Practitioner Database for their case-control study of breast cancer and prior use of medications, including ACE-I. In other studies, subjects were apparently selected by participating physicians, and thus may not be representative of all subjects taking a specific drug.^{138, 142, 144, 147, 150}

Withdrawal rates

Total withdrawal rates varied across studies examining ACE-Is, with the lowest rate 3.3%¹⁴³ in a study of heart failure patients on enalapril with 3-month follow-up. In this study it is unclear how closely the accessible population matches the recruited population, although the large sample size (more than 17 000) suggests that the study population is likely representative of the target

population. On the other hand, 2 studies reported much higher total withdrawal rates: 19.7% with trandolapril¹⁴⁴ and 25% with captopril,¹³⁹ both studies with 6 months of follow-up.

Withdrawal rates due to adverse events also varied across studies, but were generally quite low, ranging from 1.4% with enalapril at 3 months¹⁴³ to 8.1% at 6 months for nonserious events (cough, nausea, headache) and an additional 0.9% due to serious adverse events with trandolapril.¹⁴⁴

Rates of total withdrawals with AIIRAs were infrequently reported: 1 study reported 17.5% with 6 or more months of losartan,¹⁴⁸ and a second study 19.9% after 6 months on valsartan.¹⁴⁶ Both of these studies recruited subjects who were not selected,^{146, 148} but rather were likely representative of the target populations. Withdrawals due to adverse events with AIIRAs were infrequent: 5.1% (losartan¹⁴⁸) and 4.0% (telmisartan¹⁵¹).

Adverse events

We confined our review to examination of serious harms, as noted in the Methods Section, and defined these as events that required unanticipated and/or urgent medical treatment.

Data on specific, serious adverse events are reported in Table 6. Angioedema was rare in both ACE-I and AIIRAs, although few studies reported on this event. Rates in ACE-I were 0.02% (captopril),¹³⁹ and 0.004% in men and 0.02% in women (perindopril).¹³⁸ In this study of perindopril, the overall incidence of allergic reactions (both serious and nonserious) was 0.02%. In AIIRAs, rates were 0.03% (valsartan¹⁴⁶) and 0.06% (losartan¹⁴⁸). In studies reporting the timing of onset of angioedema, a median time of 28 day (range 7 to 306) was noted with captopril¹³⁹ and 14 days with perindopril.¹³⁸

Serious renal adverse events

In ACE-I, very few serious renal effects were reported. Hyperkalemia was noted in 0.13% in 1 study or enalapril.¹⁴³ Renal failure was listed as a cause of death in 21 of 67 000 patients on captopril, with all cases having underlying renal disease.¹³⁹ Serum creatinine rose from ≤ 1.2 mg/dL to > 2.5 mg/dL in 0.2% in a large study (N=18 977) focused on renal function changes with lisinopril,¹⁴⁵ with a reason other than the study drug identified for the increase in most patients (e.g., sepsis). In another large study, renal dysfunction occurred in 0.14% of men and 0.17% of women taking perindopril, with 3 cases of chronic kidney disease referred for hemodialysis (2 had renal artery stenosis).¹³⁸

Few data were reported on renal effects of AIIRAs. With 6 or more months of losartan,¹⁴⁸ the incidence density per 1000 patient-months of renal dialysis was 13 at month 1 and 2 at months 2 to 5. These researchers were unable to differentiate the etiology of renal failure and electrolyte abnormalities due to the drug from that due to pre-existing disease.

Serious cardiovascular adverse events

Rates of hypotension were reported at 0.3% with ACE-I, including captopril,¹³⁹ cilapapril,¹⁴² enalapril,¹⁴³ and perindopril.¹³⁸ Rates of postural or other significant hypotension were not reported in the studies of AIIRAs that we examined. Rates of cardiovascular disease events were reported in several studies, but no study compared rates to expected rates in similar, general populations.

Deaths

Mortality rates were $\leq 3.0\%$ and no study of either ACE-I or AIIRAs attributed death to 1 of these drugs. In a large cohort of hypertensive patients taking captopril,¹³⁹ the death rate of 1.1% was 80% of the expected rate (in general populations) and 4% more than expected rate of cardiovascular deaths in general populations. No other study provided such comparative data.

Other serious adverse events

A case-control study examined the incidence of breast cancer in users compared with nonusers of captopril, lisinopril, and enalapril, and the odds of breast cancer were not significantly different with any of these 3 drugs compared with nonusers.¹⁴¹

Two studies of ACE-I reported rates of serious hematologic events. Chalmers and colleagues¹³⁹ (N=16 698) reported 15 cases of significant hematological disorders with captopril, with 15 patients withdrawing because of these: 11 with leucopenia and 4 with thrombocytopenia. None of these disorders persisted after captopril withdrawal and several of the cases had other likely causes. Speirs and coauthors¹³⁸ reported 3 cases of nonfatal thrombocytopenia with perindopril (N=47 351).

Adverse events in subpopulations

Few studies examined subgroups based on age or and sex;^{138, 139, 148, 151} no study examined racial/ethnic groups. Chalmers and colleagues¹³⁹ noted that withdrawals from captopril-related adverse events were more frequent in women over 70 years of age (10.4%) than in other demographic subgroups (no statistics reported). On the other hand, another large, a post-marketing study reported that withdrawal rates due to adverse events related to perindopril were not different across age and sex groups except for withdrawals due to renal insufficiency which increased with age (the rate was highest in men over 80 years of age).¹³⁸

In another post-marketing study, the incidence density for dizziness, edema, and nausea/vomiting were higher for patients 76 years of age and older compared with younger persons. The rates of other nonserious adverse events were similar among age groups.¹⁴⁸

In a meta-analysis of 30 trials and 20 open-label studies of telmisartan,¹⁵¹ the authors reported that the incidence of all-cause adverse events per person-year was lower in persons over 65 years of age than younger persons, although serious adverse events occurred at a higher rate in the older age group (no statistics reported).

No study compared the effect of comorbid conditions (in addition to the indication for the ACE-I or AIIRA) on adverse event rates. One study included subjects with hypertension and type 2 diabetes mellitus taking irbesartan with or without hydrochlorothiazide,¹⁴⁷ but no comparisons among comorbidities were made. In this study, 62 adverse events were noted in 48 patients (0.3% of total study population): 2 were deemed serious, including renal insufficiency and tremor. The latter event was considered likely related to the study medication.

Table 6. Observational studies of ACE-I and AIIRA drugs

Study Country	Total N Follow-up period Population	Intervention drug	Total withdrawals Withdrawals due to AEs	Renal, hepatic, and metabolic adverse events	Cardiovascular adverse events and deaths	Other adverse events
ACE-I						
Captopril						
Chalmers 1992 ¹³⁹ Scotland	67 698 Median follow-up 6 months; total 39 635 patient-years Hypertension	Captopril, dosage NR	75% of patients completed the study Withdrawal due to AEs: 8.2%	Liver disease: 9 patients withdrew; all had other likely causes; 3 deaths from liver failure (not suspected to be related to drug) Renal failure: listed as cause in 21 deaths; all had underlying disease	Hypotension: 2.8/1000 (more common in >70y) Deaths: 1.1%; this rate was 80% of expected rate (in general populations) and 4% more than expected rate of CV deaths in general populations	Angioedema: 16 patients (0.02%); after median 28 day (range, 7-306 days) Hematological disorders: 15 patients withdrew due to heam disorders; 11 leucopenia; 4 thrombocytopenia; none persisted after withdrawal; several cases had other likely causes
Gonzalez-Perez 2004 ¹⁴¹ Sweden	Total on ACE about 1000 NR NR	Captopril, enalapril, lisinopril dosages NR	NA (case-control)	NR	NR	Incidence breast cancer among current users of ACE-I vs. non-users: Captopril Usage <2 years: OR, 1.1 (95% CI, 0.6 to 2.0) Usage >2 years: OR, 0.8 (95% CI, 0.5 to 1.3) Enalapril Usage <2 years: OR, 0.9 (95% CI, 0.6 to 1.4) Usage >2 years: OR, 0.7 (95% CI, 0.5 to 1.1) Lisinopril Usage <2 years: OR, 0.8 (95% CI, 0.5 to 1.2) Usage >2 years: OR, 0.7 (95% CI, 0.7 to 1.6)

Study Country	Total N Follow-up period Population	Intervention drug	Total withdrawals Withdrawals due to AEs	Renal, hepatic, and metabolic adverse events	Cardiovascular adverse events and deaths	Other adverse events
DiBianco 1991¹⁴⁰ US	6669 (with data) 8 weeks HF: mild-to-moderate	Captopril: start at 12.5 mg tid, titrate up to 15 mg tid Mean dosage: 65 mg QD	Total withdrawals: 14.8% Of patients with AEs, 4.9% withdrew	NR	Deaths: 3.0%, causes NR Postural hypotension: <1%	AEs (1 or more) in 18.1% of patients Total AEs: 1983 in 1386 patients)
Cilazapril						
Rosenthal 1996¹⁴² Germany	33841 3 months Hypertension	Cilazapril: start at 1.25 mg qd, increase to 2.5 to 5 mg qd Median dosage at end of observation period: 2.5 mg qd	Total withdrawals: 6.7% Withdrawal due to AEs: 3.7%	NR	Deaths: 44 patients (12 cardiac, 10 cerebral) Hypotension (not defined): approximately 0.2% (graphical data)	Overall rate of AEs: 7.3%; 3.8% of total population considered to have drug-related AE
Enalapril						
Messner 1995¹⁴³ France	17546 3 months HF (mild-to-moderate)	Enalapril: start 2.5 mg qd, titrate up to 20 mg qd Mean daily dosage 16 mg	Total withdrawals: 3.3% Withdrawal due to AEs: 1.4%	Hyperkalemia: 0.13%	Hypotension: 0.34% Postural hypotension: 0.3% Death: 0.72%; none felt related to drug Worsening HF: 0.54%; none felt related to drug MI: 0.10% Pulmonary embolism: 0.08%	Overall adverse event rate: 5.6%

Study Country	Total N Follow-up period Population	Intervention drug	Total withdrawals Withdrawals due to AEs	Renal, hepatic, and metabolic adverse events	Cardiovascular adverse events and deaths	Other adverse events
Lisinopril						
Thorp 2005 ¹⁴⁵	13166	Lisinopril; dosage NR	NA: only subjects with pre and post creatinine levels were examined	Rise in serum creatinine from ≤ 1.2 mg/dL to >2.5 mg/dL: 31 patients (0.2%) Rise in serum creatinine from ≤ 1.2 mg/dL to >1.2 mg/dL: 6.8%	Deaths: 3 patients	NR
US	6 months Various indications			In N=31: possible contributors to increase in creatinine: CHF (9/31), dehydration 7/31, infection 4/31 In N=31, "most patients" had decrease		
Perindopril						
Speirs 1998 ¹³⁸	47 351	Perindopril: started at 2 (>70 y) to 4 mg and titrated up to 8 mg	Total withdrawals: 8% Withdrawal due to AEs: Female: 6.3% Male: 3.5%	Renal dysfunction: men 0.14%, women 0.17%; 3 cases of CKD referred for hemodialysis (2 had renal artery stenosis)	Deaths: 190 (0.4%) 27 due to MI; 26 due to stroke Hypotension: men 0.29%, women 0.4%; 1 case related to nonfatal stroke	Overall rate of AEs: men 14.2%, women 17.8% Hospital admissions: 255 Angioedema: men 0.004%, women 0.02% Serious allergic reaction: men 0.02%, women 0.01%; 3 cases were pancytopenia which started after perindopril started Hematologic disturbance: men 0.02%, women 0.004%
United Kingdom	12 months Hypertension					

Study Country	Total N Follow-up period Population	Intervention drug	Total withdrawals Withdrawals due to AEs	Renal, hepatic, and metabolic adverse events	Cardiovascular adverse events and deaths	Other adverse events
						Serious allergic reaction: men 0.02%, women 0.01%
Trandolapril						
Tytus 2007¹⁴⁴	2096	Trandolapril: 1 mg qd, titrated up to 4 mg qd	Total withdrawal during 14-week titration period 413/2096 (19.7%)	NR	NR	Total of 343 AEs attributed to study drugs in 252 patients (15.3%)
Canada	26 weeks		Withdrawal during remaining 12 weeks: 33/1683 (2%)			Serious AEs: pregnancy, cerebral aneurysm, diabetic crisis, TIA, carcinoma, others (rates NR)
	Hypertension		Withdrawal due to serious AE: 19 (0.9%) Withdrawal due to nonserious AE: 169 (8.1%) (cough, nausea, headache)			None attributed to trandolapril
AIRAs						
Irbesartan						
Bramlage 2004¹⁴⁷	17 284	Irbesartan 300 mg qd (Aprovel 300) or combined with HCTZ 12.5mg qd (CoAprovel 300)	Data available on 96.0%; no other details	Terminal renal insufficiency, 1 subject, "not related to study medication"	No deaths during study	62 AEs noted in 48 patients (0.3% of total) 2 serious AEs: terminal renal insufficiency "not related to study medication" and tremor "likely related"
Germany	3 months					
	Hypertension and DM2					

Study Country	Total N Follow-up period Population	Intervention drug	Total withdrawals Withdrawals due to AEs	Renal, hepatic, and metabolic adverse events	Cardiovascular adverse events and deaths	Other adverse events
Mann 1999 ¹⁴⁸	14 522	Losartan, dosage NR	Survey response rate 60%; additional 7.8% had no event data; useful information obtained on 14 522 subjects Total withdrawals: 17.5% after 6 months Withdrawal due to AEs: 5.1%	Renal dialysis: incidence density per 1000 patient/months: month 1: 13; month 2-5: 2 Renal failure and electrolyte abnormalities: researchers unable to differentiate from pre-existing disease	Incidence density: month 1; month 2-5 Cardiac failure: 53; 115 Number of cases: Death: 363; none attributed to losartan	303 adverse drug reactions (defined as attributed to the drug by the general practitioner) (including dizziness, headache, malaise, nausea, cough, etc) Number of cases: Angioedema: 8 (0.06%)
United Kingdom	6+ months Hypertension or HF					
Schrader 2007 ¹⁵⁰	14 200	Irbesartan 75 to 300 mg daily or irbesartan/HCTZ 150/12.5 or 300/12.5 mg qd	Total withdrawal: NR Withdrawal due to AEs: NR	NR	Number of patients (N=14 200) Deaths: 16 over 9-m follow-up Cardiogenic shock: 1 MI: 2	Overall AE rate: 0.62% (141 events in 88 patients) Serious AEs (not defined): 34 patients (0.24%) (not all were listed in table or described) Cerebral infarction: 1 Gastrointestinal hemorrhage: 1
Germany	Up to 9 months Hypertension					
Olmesartan						
Schmidt 2008 ¹⁴⁹	4252	Olmesartan 10 to 40 mg qd; mean dosage 19.9 (SD 7.1) mg	Total withdrawal: NR Withdrawal due to AEs: NR	NR	Serious AEs (not defined): 2 patients: circulatory collapse and aortic bypass surgery	Overall AE rate: 0.66%
Germany	Mean follow-up 44.1 days Hypertension					

Study Country	Total N Follow-up period Population	Intervention drug	Total withdrawals Withdrawals due to AEs	Renal, hepatic, and metabolic adverse events	Cardiovascular adverse events and deaths	Other adverse events
Telmisartan						
Schumacher 2008¹⁵¹	5013 for telmisartan monotherapy in RCTs; 5907 in open-label studies	Telmisartan 20-160 mg +/- HCTZ 6.25 to 25 mg qd or placebo	Treatment discontinuations due to AEs: Double-blind studies: 0.33 PPY (4.4%) with placebo, 0.14 PPY (2.6%) with monotherapy	Hepatobiliary laboratory abnormalities: <0.05% with monotherapy	Open-label studies, events PPY with monotherapy MIs: 0.004, (0.3%) Deaths: overall 0.004 PPY with monotherapy	AEs PPY in double-blind/open label studies: Monotherapy 2.03 (37.4%)/0.65 (49.6%), Placebo 2.73 (36.1%) Serious AEs: Monotherapy 0.07 (1.2%)/0.07 (4.4%) Placebo 0.09 (1.2%)
Italy	Varied across studies: 7 days to 2 years Hypertension		Open-label studies 0.07 PPY (4.0%)			NSD between active treatment groups in double-blind studies
Valsartan						
Biswas 2002¹⁴⁶	12881	Valsartan: dosage NR	Return rate on questionnaires: 55%	Abnormal liver function tests: 0.2% (1 case of jaundice and 1 of hepatitis improved after stopping the drug)	Deaths: 1.5% (78/85 due to CVD or cancer)	Total AEs: 295 events in 209 (1.5%) of patients Most common reasons for withdrawal due to AEs: malaise (0.3%), dizziness (0.1%)
United Kingdom	6+ months Hypertension		Withdrawal at 6 month follow-up: 19.9%	Hyperkalemia: 0.13% Hyponatremia: 0.12%		Angioedema: 0.03% Spontaneous bleeding: hematuria, hemoptysis, ect: 59 cases; unclear if related to drug

Abbreviations: AE, adverse event; CKD, chronic kidney disease; CVD, cardiovascular disease; DM2, type 2 diabetes mellitus; HCTZ, hydrochlorothiazide; HF, heart failure; MI, myocardial infarction; NA, not applicable; NR, not reported; NSD, no significant difference; OR, odds ratio; PPY, per person year; qd, once daily; RCT, randomized controlled trial.

CONCLUSIONS AND LIMITATIONS

AIIRA drugs are not significantly different from, nor are they inferior to, ACE-I drugs for a broad range of patient-important effectiveness outcomes. These include cardiovascular events, mortality, quality of life, renal function, and symptoms. This conclusion applies to both monotherapy and combination therapy with ACE-Is and ARBs, and across a broad range of populations including those with heart disease, diabetic proteinuria, nondiabetic proteinuria, chronic kidney disease, and hypertension. Combination therapy with an ACE-I and an ARB, does, however, produce a reduction in proteinuria in nondiabetic proteinuria or chronic kidney disease. Rates of cough and withdrawal were generally less with ARBs than ACE-Is, and hypotension was more common with combination therapy.

Aliskirin administered with an ACE-I or ARB decreased mean urinary albumin-to-creatinine ratio in 1 study, but did not improve other renal outcomes or withdrawal rates in either available study.

There are a number of important limitations for this review. Although we attempted to compare specific ACE-Is with specific ARBs, few studies were available for many of these comparisons. If there are important intra-class differences among ACE-Is or ARBs, then valid conclusions about inter-class comparisons are limited.

Additionally, little evidence was available for evaluating inter-class differences between DRI, ACE-I and AIIRA drugs in subgroups based on age, sex, race, other medications or comorbidities. For example, only 3 trials (< 5%) evaluated the impact of race on treatment effects, which did not provide sufficient evidence to reliably determine the comparative effectiveness and harms for most comparisons.

The data and conclusions concerning populations with cardiovascular disease including heart failure are likely applicable to broad clinical populations due to the large sample size and relatively unselected populations in a number of these trials. For populations with hypertension, nondiabetic proteinuria, chronic kidney disease, and diabetic nephropathy, the small trials with selected populations may not be applicable to populations seen in general clinical practice.

SUMMARY

The evidence is summarized in Table 7, below.

Table 7. Summary of the evidence^a

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Key Question 1. What are the comparative effectiveness/efficacy and harms between aliskiren and placebo?			
1a. When used as monotherapy?			
1b. When used in combination with angiotensin converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (AIIRA) drugs?			
DIABETIC NEPHROPATHY			
Aliskiren plus losartan vs.	1 trial, N=599	NA, Fair	As compared with losartan monotherapy, dual therapy with aliskiren plus losartan significantly

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
losartan monotherapy			reduced the mean urinary albumin-to-creatinine ratio by 18% after adjustment for SBP change (95% CI, 7 to 28). There was no significant difference between dual therapy and monotherapy on mean rate of change in eGFR (-1.4 vs. -3.8; <i>P</i> =0.07). There were no significant differences between dual therapy and losartan monotherapy in overall withdrawals (14% vs. 11%), overall adverse events (66.8% vs. 67.1%), withdrawals due to adverse events (5.6% vs. 6.4%), or for any individual adverse events.
HEART FAILURE			
Aliskirin compared with placebo (combination therapy with ACE-I or ARB)	1 trial, N=302	NA, Fair	In patients with heart failure and hypertension on an ACE-I or an ARB, there was no significant difference between aliskiren and placebo after 3 months in serum creatinine, overall withdrawals, withdrawals due to adverse events, or individual adverse events.
Key Question 2. What are the inter-class comparative effectiveness/efficacy between DRI, AIIRAs and ACE-Is?			
2a. When used as monotherapy			
2b. When used in combination with one another			
HEART FAILURE AND CARDIOVASCULAR DISEASE (HF and CVD): Monotherapy and combination therapy			
HF and CVD: Mortality and composite outcomes including mortality			
Candesartan vs. enalapril vs. combination	Heart failure 1 trial (RESOLVD) N=768	NA Study quality: Fair	Overall summary Monotherapy: AIIRA not inferior to ACE-I (2 trials); AIIRA similar to ACE-I for primary composite outcomes or for mortality (5 trials); earlier ELITE trial reported benefit for losartan vs. captopril for sudden cardiac death. Combination therapy: AIIRA similar to ACE-I (3 trials)
Irbesartan vs. ramipril (monotherapy combined with diuretic)	Heart failure 1 trial N=150	NA Study quality: Fair	Specific comparisons Candesartan vs. enalapril: NSD among groups for rates of death. 43-week follow-up (trial stopped early). Irbesartan vs. ramipril: NSD in deaths.
Losartan vs. captopril (monotherapy)	Heart failure: ELITE and ELITE II Acute MI with HF or new Q-wave anterior wall MI: OPTIMAAL 3 trials N=9351	GRADE: All-cause mortality, CV deaths, sudden death, CVD events: moderate	Losartan vs. captopril: In the earlier trial (ELITE), death and/or heart failure admissions were decreased with losartan (<i>P</i> =0.075), primarily due to decrease in sudden cardiac deaths. Subsequent 2 trials did not substantiate this difference. In all 3 trials there was NSD between groups in all-cause mortality at follow-up to 2.7 years. Cardiovascular death was more common with losartan than captopril (<i>P</i> =0.032) in OPTIMAAL.
Telmisartan vs. ramipril vs. combination	Vascular disease or diabetes with end-organ damage but without symptomatic heart failure 1 trial	NA Study quality: good	Telmisartan not inferior to ramipril for primary

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
	(ONTARGET) N=25620		composite outcome (death from cardiovascular causes, MI, stroke, or hospitalization for HF). Combination therapy: NSD from ramipril alone for the primary outcome.
Valsartan vs. captopril vs. combination	Recent, acute MI complicated by HF or evidence of LVSD 1 trial (VALIANT) N=14703	NA Study quality: good	Valsartan vs. captopril: NSD in death rates between monotherapies or between combination therapy and captopril; valsartan not inferior to captopril for mortality ($P=0.004$) and for composite endpoint of fatal and nonfatal CV events ($P<0.001$).
HF and CVD: Renal			
Candesartan vs. enalapril vs. combination	Heart failure 1 trial (RESOLVD) N=768	NA Study quality: Fair	Overall summary Monotherapy: AIIRA are not significantly different from ACE-I (2 trials) Combination therapy: renal outcomes significantly worse than ACE-I or AIIRA alone (1 study)
Telmisartan vs. ramipril vs. combination	Vascular disease or diabetes with end-organ damage but without symptomatic heart failure 1 trial (ONTARGET) N=25620	NA Study quality: good	Specific comparisons Candesartan vs. enalapril: NSD among groups in renal dysfunction at 43-week follow-up (trial stopped early). Telmisartan vs. ramipril: For the primary renal composite outcome (dialysis, doubling of creatinine, or death) event rates were similar. Composite outcome increased with combination therapy ($P=0.037$).
Candesartan vs. enalapril vs. combination	Heart failure 1 trial (RESOLVD) N=768	NA Study quality: Fair	
HF and CVD: Quality of life, symptoms, hospitalizations			
Candesartan vs. enalapril vs. combination	Heart failure 1 trial (RESOLVD) N=768	NA Study quality: Fair	Overall summary AIIRA drugs are not significantly different from, nor are they inferior to, ACE-I drugs for quality of life (8 studies), exercise capacity or symptoms (3 studies), hospital admissions for heart failure (8 studies). No benefit for combination therapy (1 study).
Irbesartan vs. ramipril (monotherapy combined with diuretic)	Heart failure 1 trial N=150	NA Study quality: Fair	Specific comparisons Candesartan vs. enalapril: NSD among groups for the 6-minute walk test; NYHA classification; rates heart failure or other hospitalizations; quality of life at 43-week follow-up (trial stopped early). Irbesartan vs. ramipril: NSD in quality of life or rates of hospitalization.
Losartan vs. captopril (monotherapy)	Heart failure: ELITE and ELITE II Acute MI with HF or new Q-wave anterior wall MI: OPTIMAAL 3 trials N=9351	GRADE: hospital admissions: moderate NYHA class, quality of life: high	Losartan vs. captopril: NSD between groups in any outcome, including total hospital admissions, admissions for heart failure, or health related quality of life at follow-up to 2.7 years.
Losartan vs. enalapril (monotherapy and combination therapy)	Heart failure Monotherapy: 3 trials (+ 2 poor quality), combination	GRADE: Quality of life and exercise capacity: low	Losartan vs. enalapril: Exercise capacity improved with both losartan and enalapril

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
	therapy: 1 trial N=302 (excluding poor quality studies)		monotherapy, with NSD groups (2 studies). Effect on HF symptoms inconsistent (2 studies). Quality of life: no significant improvement with monotherapy or combination therapy vs. placebo (1 study).
Telmisartan vs. enalapril (monotherapy plus diuretic)	Heart failure 1 trial (REPLACE) N=378	NA Study quality: fair	Telmisartan vs. enalapril: NSD within or between treatments with continuation of enalapril vs. switching to telmisartan at 12 weeks of follow-up for exercise duration, NYHA classification, or quality of life.
Telmisartan vs. ramipril vs. combination	Vascular disease or diabetes with end-organ damage but without symptomatic heart failure 1 trial (ONTARGET) N=25620	NA Study quality: good	Telmisartan vs. ramipril: Telmisartan not inferior to ramipril for admissions for heart failure; combination therapy not significantly different from ramipril for heart failure admissions. Valsartan was not inferior to enalapril in exercise capacity at 12-weeks follow-up. Quality of life and symptom assessment were similar between groups.
Valsartan vs. captopril vs. combination	Recent, acute MI complicated by HF or evidence of LVSD 1 trial (VALIANT) N=14703	NA Study quality: good	Valsartan vs. captopril: NSD in quality of life and hospitalization rates among the treatment groups.
Valsartan vs. enalapril (monotherapy)	Heart failure 1 trial (HEAVEN) N=141	NA Study quality: fair	
HYPERTENSION: Monotherapy			
Hypertension-monotherapy: Mortality			
Eprosartan vs. enalapril	2 trials, N=853	Low	Only reported in 8 (N=3492) of 22 trials. None were powered to measure all-cause mortality as a primary outcome. No deaths were reported for valsartan or ramipril groups over 12 months in the longest-term trial (N=369). Event rates ranged from 0% to 2% in the shorter-term trials, with most trials reporting no events, and there were no significant differences between AIIRA and ACEI in any trial.
Valsartan vs. lisinopril	2 trials, N=1346	Moderate	
Losartan vs. fosinopril	1 trial, N=33	NA, (Good=1, Fair=4)	
Valsartan vs. benazepril	1 trial, N=90		
Valsartan vs. ramipril	1 trial, N=369		
Telmisartan vs. ramipril	1 trial, N=801		
Hypertension-monotherapy: CV events			
Valsartan vs. ramipril	1 trial, N=369	NA (Fair=1)	Atrial fibrillation recurrence was significantly lower for valsartan (16%) vs. ramipril (28%), $P<0.05$.
Hypertension-monotherapy: Change in renal function (serum creatinine, creatinine clearance, GFR, albumin)			
Losartan vs. enalapril	3 trials, N=486	Low	11 trials (N=1506) did not consistently demonstrate significant differences related to renal function for AIIRAs vs. ACE-Is. In the only
Losartan vs. captopril	1 trial, N=396	NA (Good=1,	

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Losartan vs. fosinopril	1 trial, N=33	Fair=7)	trial (N=50) that reported GFR, increases were 12% for losartan and 5% for enalapril over 3 years (statistical analysis not reported). For serum creatinine, changes were consistently minimal (-3% to +8%) across 7 short-terms trials that ranged in duration from 3 to 6 months. For creatinine clearance, changes were minimal in 2 trials (N=80) in adults without additional risk factors, but were larger for losartan and fosinopril in a trial in participants with comorbid diabetes (-34% vs. -17%). For albumin, 6 trials (N=539) did not consistently demonstrate significant differences between AIIRA and ACEI comparators
Losartan vs. perindopril	1 trial, N=85		
Losartan vs. ramipril	1 trial, N=51		
Candesartan vs. perindopril	1 trial, N=96		
Candesartan vs. lisinopril	1 trial, N=70		
Valsartan vs. benazepril	1 trial, N=156		
Valsartan vs. lisinopril	1 trial, N=133		
Hypertension-monotherapy: Quality of life			
Candesartan vs. enalapril	2 trials, N=585	Low	5 trials (N=1095) did not consistently demonstrate significant differences related to quality of life for AIIRAs vs. ACE-Is
Candesartan vs. perindopril	1 trial, N=96	NA (Fair=3)	
Eprosartan vs. enalapril	1 trial, N=136		
Telmisartan vs. enalapril	1 trial, N=278		
Hypertension-monotherapy: Overall withdrawals			
Eprosartan vs. enalapril	3 trials, N=999	Moderate	In 12 trials (N=4756), overall withdrawal rates ranged from 4% to 19% for AIIRAs and from 4% to 25% for ACE-Is and differences were consistently nonsignificant.
Valsartan vs. lisinopril	2 trials, N=1346	High	
Candesartan vs. lisinopril	1 trial, N=70	NA (Good=1 trial, Fair=7 trials)	
Losartan vs. captopril	1 trial, N=396		
Losartan vs. enalapril	1 trial, N=407		
Telmisartan vs. enalapril	1 trial, N=278		
Telmisartan vs. ramipril	1 trial, N=801		
Valsartan vs. benazepril	1 trial, N=90		
Valsartan vs. ramipril	1 trial, N=369		
HYPERTENSION: Combination therapy			
Hypertension-Combination Therapy: Change in microalbuminuria			
Valsartan-plus-benazepril vs. valsartan or benazepril monotherapies	1 trial, N=90	NA (Good=1 trial, Fair=2 trials)	Significantly greater reduction with AIIRA/ACE-I combination therapy than with ACE-I monotherapy in 3 of 3 trials. Compared with AIIRA monotherapies, significantly greater reduction with valsartan/benazepril and losartan/ramipril, but not valsartan/lisinopril combination therapy.
Losartan-plus-ramipril vs. losartan and ramipril monotherapies	1 trial, N=51		

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Valsartan-plus-lisinopril vs. valsartan or lisinopril monotherapies	1 trial, N=133		
NONDIABETIC PROTEINURIA AND CHRONIC KIDNEY DISEASE (CKD)-Monotherapy			
Nondiabetic proteinuria/CKD-Monotherapy: Composite renal endpoint			
Benazepril vs. losartan	1 trial	NA grade; Good quality	Differences in the risk of progression to composite renal endpoint were not found.
Nondiabetic proteinuria/CKD-Monotherapy: Reduction in proteinuria			
Lisinopril vs. losartan	1 trial, N=10	NA grade; Fair quality	10 of 14 trials did not find a difference between ACEI and AIIRA in the reduction of proteinuria. 8 of these trials provided statistical analysis, and 6 of those trials with analysis found p values not significant between ACEI and AIIRA for reduction in proteinuria. The 2 trials that showed a difference had <i>P</i> values of 0.05 and 0.02 favoring ACEI for proteinuria reduction. Among the 6 trials without statistical analysis, 4 showed similar percent reductions in proteinuria for ACEI (ranging from 13-60% reduction) and AIIRA (ranging from 25% to 48% reduction). 3 of 14 trials did not demonstrate equivalent blood pressure control between groups.
Enalapril vs. losartan	3 trials, N=145	LOW grade	
Benazepril vs. losartan	2 trials, N=390	LOW grade	
Ramipril vs. valsartan	2 trials, N=98	LOW grade	
Enalapril vs. telmisartan	1 trial, N=71	NA grade; Fair quality	
Trandolapril vs. losartan	1 trials, N=62	NA grade; Fair quality	
Trandolapril vs. Candesartan	1 trial, N=62	NA grade; Fair quality	
Perindopril vs. losartan vs. Candesartan	1 trial, N=62	NA grade; Fair quality	
Lisinopril vs. candesartan	1 trial, N=46	NA grade; Fair quality	
Benazepril vs. valsartan	2 trials, N=60	LOW grade	
Fosinopril vs. irbesartan	1 trial, N=11	NA grade; Fair quality	
Nondiabetic proteinuria/CKD-Monotherapy: Change in renal function (including CrCl, creatinine, and GFR)			
Lisinopril vs. losartan	1 trial, N=10 (CrCl)	NA grade; Fair quality	14 trials examined measures of renal function and found either no significant difference between treatment groups, or no significant change in these values overall during the study compared to baseline within groups. 12 of the 14 reported CrCl, 2 reported creatinine, and 3 reported GFR – several trials reported 2 methods of renal assessment. 7 of these 14 trials did analysis to examine differences in measures of renal function between treatment groups, and found no significant difference in change in renal function for ACEI vs. AIIRA. The remaining 7 trials reported no significant change from baseline to end of study in measures of renal function for either treatment group.
Enalapril vs. losartan	3 trials, N=145 (all CrCl)	VERY LOW	
Benazepril vs. losartan	2 trials, N=390 (CrCl both trials, 1 trial also GFR, 1 trial also creatinine)	LOW	
Perindopril or trandolapril vs. candesartan or losartan	1 trial, N=62 (CrCl)	NA grade; Fair quality	
Lisinopril vs. candesartan	1 trial, N=46 (CrCl)	NA grade; Fair quality	
Lisinopril vs. valsartan	1 trial, N=37 (GFR)	NA grade; Fair quality	

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Benazepril vs. valsartan	1 trial, N=24 (CrCl)	NA grade; Fair quality	
Ramipril vs. valsartan	2 trials, N=98 (one trial used CrCl and creatinine, the other used GFR)	LOW	
Enalapril vs. telmisartan	1 trial, N=71 (CrCl)	NA grade; Fair quality	
Fosinopril vs. irbesartan	1 trial, N=11 (CrCl)	NA grade; Fair quality	
NONDIABETIC PROTEINURIA AND CHRONIC KIDNEY DISEASE (CKD)-Combination Therapy			
Nondiabetic proteinuria/CKD-Combination Therapy: Composite renal endpoint			
Candesartan and benazepril vs. candesartan alone (Renal survival endpoint)	1 trial, N=86	NA grade; Fair quality	No significant difference was noted between treatment groups for renal survival endpoint, but no participants reached threshold for renal survival endpoint in either group.
Valsartan and benazepril vs. valsartan alone (Acute renal dysfunction endpoint)	1 trial, N=109	NA grade; Fair quality	No significant difference was noted between treatment groups for acute renal dysfunction endpoint, but no participants in either group experienced an acute renal dysfunction event
Nondiabetic proteinuria/CKD-Combination Therapy: Reduction in proteinuria			
Lisinopril with losartan	1 trial, N=10	NA grade; Fair quality	11 of 16 trials found greater proteinuria reduction with combination therapy vs. monotherapy, all of which reported statistical analysis. 10 trials compared combination therapy of ACEI and AIIRA vs. monotherapy; 9 of these trials showed significantly greater reduction in proteinuria with combination therapy. 6 trials compared combination therapy of ACEI and AIIRA vs. ACEI or AIIRA, 4 of which favored combination therapy for proteinuria reduction. 10 of these 16 trials demonstrated equivalent blood pressure control between treatment groups.
Enalapril with losartan	2 trials, N=105	LOW grade	
Benazepril with losartan	2 trials, N=60	LOW grade	
Lisinopril with candesartan	1 trial, N=46	NA grade; Fair quality	
Benazepril with valsartan	2 trials, N=60	VERY LOW grade	
Fosinopril with Irbesartan	1 trial, N=11	NA grade; Fair quality	
Ramipril with valsartan	1 trial, N=18	NA grade; Fair quality	
Lisinopril with losartan vs. Lisinopril	1 trial, N=17	NA grade; Fair quality	
Ramipril with candesartan vs. ramipril	2 trials, N=77	LOW grade	
Ramipril with Irbesartan vs. ramipril	1 trial, N=41	NA grade; Fair quality	
Benazepril with candesartan vs. candesartan	1 trial, N=86	NA grade; Fair quality	

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Benazepril with valsartan vs. valsartan	1 trial, N=109	NA grade; Fair quality	
Nondiabetic proteinuria/CKD-Combination Therapy: Change in renal function (including CrCl, creatinine, and GFR)			
Lisinopril with losartan	1 trial, N=10 (CrCl)	NA grade; Fair quality	16 trials evaluated renal function in the setting of combination ACEI/AlIRA vs. monotherapy, 14 of which reported statistical analysis. 12 of those 14 trials noted no significant difference in renal function measures between treatment groups. 11 of 14 trials using CrCl reported no statistical difference between groups; the remaining 3 trials showed no significant change from baseline (1) or reported that CrCl values stayed "stable among all groups" (2). 2 of 3 trials reporting GFR showed no significant differences between groups, and 1 showed GFR increased statistically more in the group receiving combination therapy (p=0.017). The single trial using creatinine reported no significant difference between treatment groups.
Enalapril with losartan	2 trials, N=105 (both CrCl)	LOW grade	
Benazepril with losartan	2 trials, N=60 (both CrCl)	LOW grade	
Lisinopril with candesartan	1 trial, N=46 (CrCl)	NA grade; Fair quality	
Benazepril with valsartan	2 trials, N=60 (Both CrCl, 1 also GFR)	VERY LOW grade	
Fosinopril with irbesartan	1 trial, N=11 (CrCl)	NA grade; Fair quality	
Ramipril with valsartan	1 trial, N=18 (CrCl)	NA grade; Fair quality	
Lisinopril with losartan vs. Lisinopril	1 trial, N=17 (CrCl and GFR)	NA grade; Fair quality	
Ramipril with candesartan vs. ramipril	2 trials, N=77 (both CrCl)	LOW grade	
Ramipril with irbesartan vs. ramipril	1 trial, N=41 (CrCl)	NA grade; Fair quality	
Benazepril with candesartan vs. candesartan	1 trial, N=86 (GFR)	NA grade; Fair quality	
Benazepril with valsartan vs. valsartan (creatinine)	1 trial, N=109	NA grade; Fair quality	
DIABETIC NEPHROPATHY-Monotherapy			
Diabetic nephropathy-Monotherapy: Mortality and other CV events			
Telmisartan vs. enalapril	1 trial, N=250	NA, both fair quality	2 trials found no significant differences between AlIRAs and ACE-Is. No deaths or CV events occurred in the trial of losartan vs. enalapril. In the trial of telmisartan vs. enalapril, rates were 5% in both groups for mortality, 2.5% vs. 1.5% for CV death, 7.5% vs. 4.6% for nonfatal MI, 7.5% vs. 5.4% for congestive HF, 5% vs. 4.6% for cerebrovascular accident and 0% in both groups for kidney failure/required dialysis
Losartan vs. enalapril	1 trial, N=24		
Diabetic nephropathy-Monotherapy: Renal changes			
Losartan vs. enalapril	3 trials, N=143	Low	8 trials (N=517) consistently found no

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Candesartan vs. ramipril	1 trial, N=21	NA, All Fair	significant differences between AIIRAs and ACE-Is related to changes in GFR (4 trials, N=389), serum creatinine (6 trials, N=390), or creatinine clearance (2 trials, N=45) For GFR, changes were largest in the longest-term trial of 5 years' duration (−19.6% for telmisartan and −15.8% for enalapril. Overall, changes in GFR ranged from +2.2% to −19.6% for AIIRAs and ranged from +6.6% to −15.8% for ACE-Is.
Losartan vs. quinapril	1 trial, N=41		
Telmisartan vs. enalapril	1 trial, N=250		
Valsartan vs. benazepril	1 trial, N=20		
Valsartan vs. enalapril	1 trial, N=42		
Diabetic nephropathy-Monotherapy: Albuminuria			
Losartan vs. enalapril	3 trials, N=74	Low	No significant differences between AIIRAs and ACE-Is related to changes in albumin levels were found in 7 of 8 trials (N=395). The only significant difference was found in the shortest-term trial (4 weeks), in which the reduction of albuminuria (mg/g) was greater for losartan vs. quinapril (−93 vs. −49; <i>P</i> =0.025). But, although linear regression showed independence from differences in effects on SBP, association with differences in DBP were not analyzed.
Candesartan vs. lisinopril	1 trial, N=197	NA, All Fair	
Candesartan vs. ramipril	1 trial, N=21		
Losartan vs. quinapril	1 trial, N=41		
Valsartan vs. benazepril	1 trial, N=20		
Valsartan vs. enalapril	1 trial, N=42		
Diabetic nephropathy-Monotherapy: Proteinuria			
Candesartan vs. ramipril	1 trial, N=21	NA, Fair	No significant difference in reduction of proteinuria (19.5% vs. −14.6% g/24 hrs).
Diabetic nephropathy-Monotherapy: Overall Withdrawals			
Losartan vs. enalapril	3 trials, N=143	Low	7 trials (N=443) consistently found no significant differences between AIIRAs and ACE-Is. Withdrawal rates ranged from 0% to 26% for AIIRAs and ranged from 0% to 28% for ACE-Is.
Candesartan vs. lisinopril	1 trial, N=197	NA, All Fair	
Losartan vs. quinapril	1 trial, N=41		
Valsartan vs. benazepril	1 trial, N=20		
Valsartan vs. enalapril	1 trial, N=42		
Renal outcomes (GFR, serum creatinine, creatinine clearance)			
Candesartan+ramipril vs. candesartan or ramipril monotherapies	1 trial, N=21	NA (Good=1, Fair=4)	5 trials (N=287) consistently found no significant advantages for combination therapy related to renal function.
Candesartan+lisinopril vs. candesartan or lisinopril monotherapy	1 trial, N=197		
Irbesartan+enalapril vs. enalapril monotherapy	1 trial, N=23		
Losartan+enalapril vs. doubled enalapril	1 trial, N=26		

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Valsartan+benazepril vs. valsartan or benazepril monotherapy	1 trial, N=20		
DIABETIC NEPHROPATHY-COMBINATION THERAPY			
Diabetic nephropathy-combination therapy: Albumin/Protein			
Losartan+enalapril vs. doubled enalapril	1 trial, N=26	NA (Good=1, Fair=5)	Albuminuria: Rate of regression from microalbuminuria to normo albuminuria was reported in 1 trial (N=20) and there was no significant difference between combination therapy with valsartan+benazepril (70%) vs. valsartan monotherapy (67%) or benazepril monotherapy (83%). Otherwise, 4 of 5 trials (n=287) found a significant advantage for combination therapy in mean reduction of albuminuria. But, in only 1 (N=20) of those trials was the additional reduction in mean albuminuria (mg/24h) for valsartan+benazepril (43%) found to be independent of arterial change when compared to benazepril monotherapy. Proteinuria: In the only trial (N=21) that reported this outcome, 24-h urinary protein excretion was significantly lower with candesartan+ramipril (2.9) compared with candesartan (3.3) and ramipril (3.5) monotherapies.
Losartan+enalapril vs. losartan or enalapril monotherapy	1 trial, N=34		
Valsartan+benazepril vs. valsartan or benazepril monotherapy	1 trial, N=20		
Irbesartan+enalapril vs. enalapril monotherapy	1 trial, N=23		
Candesartan+lisinopril vs. candesartan or lisinopril monotherapy	1 trial, N=197		
Candesartan+ramipril vs. candesartan or ramipril monotherapies	1 trial, N=21		
Diabetic nephropathy-combination therapy: Overall Withdrawals			
Valsartan+benazepril vs. valsartan or benazepril monotherapy	1 trial, N=20		3 trials (N=240) consistently found no differences in rates of overall withdrawals for combination therapy (range, 0% to 27%) vs. monotherapy (range, 0% to 28%)
Irbesartan+enalapril vs. enalapril monotherapy	1 trial, N=23		
Candesartan+lisinopril vs. candesartan or lisinopril monotherapy	1 trial, N=197		
Key Question 3. What are the inter-class comparative harms between DRI, AIIRAs and ACE-Is?			
3a. When used as monotherapy			
3b. When used in combination with one another?			
HEART FAILURE AND CARDIOVASCULAR DISEASE: Monotherapy and combination therapy			
Candesartan vs. enalapril vs. combination	Heart failure 1 trial (RESOLVD) N=768	NA Study quality: Fair	Overall summary Rates of cough and withdrawal were generally less with ARBs than ACE. Hypotension was more common with combination therapy.
Irbesartan vs. ramipril (monotherapy combined with diuretic)	Heart failure 1 trial N=150	Study quality: Fair NA	Specific comparisons Captopril vs. enalapril vs. combination: NSD

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Losartan vs. captopril (monotherapy)	Heart failure: ELITE and ELITE II Acute MI with HF or new Q-wave anterior wall MI: OPTIMAAL 3 trials N=9351	NA Study quality: fair 2, good 1	symptomatic hypotension. Irbesartan vs. ramipril: No data on adverse events. Losartan vs. captopril: Withdrawals (total, due to adverse events, and due to cough) were significantly lower with losartan than captopril (3 studies). Hypotension not different between the 2 groups (2 studies).
Losartan vs. enalapril vs. combination	Heart failure Monotherapy: 3 trials (+ 2 poor quality), combination therapy: 1 trial N=302 (excluding poor quality studies)	NA Study quality: fair 2, fair-poor 1 (poor 2)	Losartan vs. enalapril: Data were sparse on AEs; minor increases in blood urea nitrogen, creatinine, and potassium (2 studies). Cough similar between drugs (1 study). Telmisartan vs. enalapril: Adverse event rates including cough were similar between telmisartan and enalapril. Telmisartan vs. ramipril: Permanent discontinuation was more common with ramipril as monotherapy or as combination therapy due to cough or angioedema than telmisartan monotherapy. More subjects stopped telmisartan due to hypotension symptoms than ramipril. Discontinuation due to hypotension, syncope, diarrhea, or renal impairment was more likely to occur with combination therapy than with ramipril monotherapy ($P<0.05$).
Telmisartan vs. enalapril (monotherapy plus diuretic)	Heart failure 1 trial (REPLACE) N=378	NA Study quality: fair	Discontinuation due to hypotension, syncope, diarrhea, or renal impairment was more likely to occur with combination therapy than with ramipril monotherapy ($P<0.05$). Valsartan vs. captopril: Discontinuation rates were higher with combination therapy than with captopril alone ($P=0.007$). Hypotension and renal disease were more common reasons for therapy discontinuation with combination therapy than with captopril ($P<0.05$). Cough was a more common reason with captopril monotherapy ($P<0.05$).
Telmisartan vs. ramipril vs. combination	Vascular disease or diabetes with end-organ damage but without symptomatic heart failure 1 trial (ONTARGET) N=25620	NA Study quality: good	Discontinuation due to hypotension, syncope, diarrhea, or renal impairment was more likely to occur with combination therapy than with ramipril monotherapy ($P<0.05$). Valsartan vs. captopril: Discontinuation rates were higher with combination therapy than with captopril alone ($P=0.007$). Hypotension and renal disease were more common reasons for therapy discontinuation with combination therapy than with captopril ($P<0.05$). Cough was a more common reason with captopril monotherapy ($P<0.05$).
Valsartan vs. captopril vs. combination	Recent, acute MI complicated by HF or evidence of LVSD 1 trial (VALIANT) N=14703	NA Study quality: good	Discontinuation due to hypotension, syncope, diarrhea, or renal impairment was more likely to occur with combination therapy than with ramipril monotherapy ($P<0.05$). Valsartan vs. enalapril: The rate of overall adverse events was similar between groups.
Valsartan vs. enalapril (monotherapy)	Heart failure 1 trial (HEAVEN) N=141	NA Study quality: fair	
HYPERTENSION: Monotherapy			
Hypertension-Monotherapy: Overall adverse events			
Eprosartan vs. enalapril	2 trials, N=863	Low	In 10 trials (N=4616), overall adverse event rates ranged widely; from 5% to 76% for AIIRAs and from 6% to 81% for ACE-Is. Rates were generally lower for AIIRAs, but differences were only significant in the 3 shortest-term trials (3 to 4 months).
Valsartan vs. lisinopril	2 trials, N=1346	Low	
Candesartan vs. enalapril	1 trial, N=429	NA (All fair quality)	
Candesartan vs. perindopril	1 trial, N=96		
Losartan vs. captopril	1 trial, N=396		

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Losartan vs. enalapril	1 trial, N=407		
Telmisartan vs. enalapril	1 trial, N=278		
Telmisartan vs. ramipril	1 trial, N=801		
Hypertension-Monotherapy: Cough			
Candesartan vs. enalapril	2 trials, N=585	Moderate	In 14 trials (N=4987), rates of cough-related adverse events were generally lower for AIIRAs (range, 0% to 35%) compared with ACE-Is (range, 4% to 68%). Differences were statistically significant in favor of AIIRAs in 9 of 14 trials. Lack of statistical significance was likely due to small sample sizes in 4 of the other 5 trials.
Eprosartan vs. enalapril	3 trials, N=999	High	
Losartan vs. enalapril	3 trials, N=486	Low	
Valsartan vs. lisinopril	2 trials, N=1346	Low	
Candesartan vs. perindopril	1 trial, N=96	NA (All fair quality)	
Losartan vs. captopril	1 trial, N=396		
Telmisartan vs. enalapril	1 trial, N=278		
Telmisartan vs. ramipril	1 trial, N=801		
Hypertension-Monotherapy: Withdrawals due to adverse events			
Eprosartan vs. enalapril	2 trials, N=665	Moderate	In 14 trials (N=4724), rates of withdrawals due to adverse events were generally similar for AIIRAs and ACE-Is, ranging from 0% to 12% in both drug groups. One exception, however, was that in the largest trial (N=1213), and the only trial rated good quality, rates were significantly lower for valsartan vs. lisinopril (1% vs. 4%, $P=0.01$).
Losartan vs. enalapril	2 trials, N=457	Moderate	
Valsartan vs. lisinopril	2 trials, N=1346	Low	
Candesartan vs. enalapril	1 trial, N=156	NA (All fair quality)	
Candesartan vs. lisinopril	1 trial, N=70		
Candesartan vs. perindopril	1 trial, N=96		
Losartan vs. captopril	1 trial, N=396		
Telmisartan vs. enalapril	1 trial, N=278		
Telmisartan vs. ramipril	1 trial, N=801		
Valsartan vs. benazepril	1 trial, N=90		
Valsartan vs. ramipril	1 trial, N=369		
HYPERTENSION: COMBINATION THERAPY			
Valsartan-plus-benazepril vs. valsartan or benazepril monotherapies	1 trial, N=90	NA (Good=1 trial, Fair=2 trials)	None of the trials reported any significant differences between AIIRA/ACE-I combination therapy groups and the AIIRA or ACE-I monotherapy groups.
Losartan-plus-ramipril vs. losartan and ramipril monotherapies	1 trial, N=51		
Valsartan-plus-lisinopril vs. losartan and lisinopril monotherapies	1 trial, N=133		
NONDIABETIC PROTEINURIA/CKD: MONOTHERAPY^c			
Nondiabetic proteinuria/CKD-monotherapy: Cough			
Benazepril vs. losartan	1 trial, N=360	NA grade; Good	1 of 3 trials found statistically greater incidence of cough in those treated with ACEI. Of the 2

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Enalapril vs. telmisartan	1 trial, N=71	quality NA grade; Fair quality	remaining studies, 1 found no cough with use of either agent, and 1 found a rate of cough of 4% for those on ACEI vs. zero for those on AIIRA.
Fosinopril vs. irbesartan	1 trial, N=11	NA grade; Fair quality	
Nondiabetic proteinuria/CKD-monotherapy: Hyperkalemia			
Lisinopril vs. losartan	1 trial, N=10	NA grade; Fair quality	3 of 5 trials found greater incidence of hyperkalemia in those treated with ACEI vs. AIIRA. One of these trials provided statistical analysis to support this difference. Among trials that reported overall numbers of events, rates of hyperkalemia for ACE ranged from 4-22% and for AIIRA ranged from 4% to 11%.
Benazepril vs. losartan	1 trial, N=360	NA grade; Good quality	
Lisinopril vs. candesartan	1 trial, N=46	NA grade; Fair quality	
Benazepril vs. valsartan	1 trial, N=24	NA grade; Fair quality	
Fosinopril vs. irbesartan	1 trial, N=11	NA grade; Fair quality	
Nondiabetic proteinuria/CKD-monotherapy: Acute kidney injury			
Benazepril vs. losartan	1 trial, N=360	NA grade; Good quality	2 of 3 trials reported higher numerical rates for those on ACEI vs. AIIRA, no statistical analyses performed. Using absolute numbers of events, the rate of AKI for those on ACE ranged from 2.8% to 18%, and for those on AIIRA was 3.3%.
Enalapril vs. telmisartan	1 trial, N=71	NA grade; Fair quality	
Fosinopril vs. irbesartan	1 trial, N=11	NA grade; Fair quality	
NONDIABETIC PROTEINURIA/CKD: Combination Therapy^c			
Nondiabetic proteinuria/CKD-combination therapy: Dizziness/light-headedness			
Lisinopril with losartan	1 trial, N=10	NA grade; Fair quality	2 of 4 trials reporting rates of dizziness or lightheadedness between treatment groups noted higher rates of dizziness/light-headedness with combination vs. monotherapy (0% to 20% with combination therapy vs. 0% to 10% with monotherapy). One trial noted no difference in rates of dizziness/lightheadedness between treatment groups. One larger trial (N=109) reported similar rates of dizziness/lightheadedness between treatment groups (4.5% to 6.8%). Statistical analysis was not provided.
Fosinopril with irbesartan	1 trial, N=11	NA grade; Fair quality	
Ramipril with irbesartan vs. ramipril	1 trial, N=41	NA grade; Fair quality	
Benazepril with valsartan vs. valsartan	1 trial, N=109	NA grade; Fair quality	
Nondiabetic proteinuria/CKD-combination therapy: Hyperkalemia			
Lisinopril with losartan	1 trial, N=10	NA grade; Fair quality	4 of 6 trials reporting rates of hyperkalemia between treatment groups noted higher rates of hyperkalemia with combination vs. monotherapy (10% to 20% with combination vs. 0% to 10% with monotherapy). One small trial (N=24) found no difference in rates of hyperkalemia between treatment groups, and 1
Fosinopril with irbesartan	1 trial, N=11	NA grade; Fair quality	
Lisinopril with candesartan	1 trial, N=46	NA grade; Fair quality	

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Benazepril and valsartan	1 trial, N=24	NA grade; Fair quality	found higher rates of hyperkalemia with ACEI (ramipril) vs. AIIRA (irbesartan) (trial with N=46). Statistical analysis was not provided.
Ramipril with irbesartan vs. ramipril	1 trial, N=41	NA grade; Fair quality	
Benazepril with valsartan vs. valsartan	1 trial, N=109	NA grade; Fair quality	
DIABETIC NEPHROPATHY: MONOTHERAPY			
Diabetic Nephropathy-Monotherapy: Overall adverse events			
Candesartan vs. ramipril	1 trial, N=21	NA, All Fair	3 of 4 trials (N=416) found no significant differences between AIIRAs and ACE-Is. However, in 1 trial (N=42) rates were significantly lower for valsartan vs. enalapril after 1 year (14% vs. 45%; $P=0.015$).
Losartan vs. enalapril	1 trial, N=103		
Telmisartan vs. enalapril	1 trial, N=250		
Valsartan vs. enalapril	1 trial, N=42		
Diabetic Nephropathy-Monotherapy: Cough			
Candesartan vs. ramipril	1 trial, N=21	NA, All Fair	In 3 of 3 trials (N=166), incidence of cough was 0% in the AIIRA groups and ranged from 5% to 35% in the ACE-I groups. The difference between AIIRA and ACE-I groups was statistically significant in the 2 larger and longer-term trials (duration=1 year), but was nonsignificant in the smaller (N=21), shorter-term trial (16 weeks).
Losartan vs. enalapril	1 trial, N=103		
Valsartan vs. enalapril	1 trial, N=42		
Diabetic Nephropathy-Monotherapy: Withdrawals due to adverse events			
Candesartan vs. lisinopril	1 trial, N=197	NA, All Fair	6 trials (N=633) consistently found no significant differences between AIIRAs (range, 0% to 17%) and ACE-Is (range, 2% to 23%)
Candesartan vs. ramipril	1 trial, N=21		
Losartan vs. enalapril	1 trial, N=103		
Telmisartan vs. enalapril	1 trial, N=250		
Valsartan vs. benazepril	1 trial, N=20		
Valsartan vs. enalapril	1 trial, N=42		
DIABETIC NEPHROPATHY: COMBINATION THERAPY			
Diabetic nephropathy-combination therapy: Overall adverse events, withdrawals due to adverse events, cough, gastrointestinal events, and hypotension			
Losartan+enalapril vs. losartan or enalapril monotherapy	1 trial, N=34	NA (Good=1, Fair=4)	5 trials (N=295) consistently found no significant differences between combination therapy and monotherapy related to harms. For withdrawals due to adverse events (3 trials, N=238), rates ranged from 0% to 5% for combination therapy, 0% to 5% for AIIRAs, and 0% to 11% for ACE-Is. For hypotension (3 trials, N=64), rates ranged from 9% to 33% for combination therapy, 0% to 5% for AIIRAs and
Valsartan+benazepril vs. valsartan or benazepril monotherapy	1 trial, N=20		
Irbesartan+enalapril vs. enalapril monotherapy	1 trial, N=23		

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
Candesartan+lisinopril vs. candesartan or lisinopril monotherapy	1 trial, N=197		0% to 11% for ACE-Is. Overall adverse event rates (2 trials, N=55) ranged from 0% to 19% in all groups. Cough was only reported in 1 trial (N=21) and was 0% for candesartan+ramipril, 0% for candesartan and 5% for ramipril.
Candesartan+ramipril vs. candesartan or ramipril monotherapy	1 trial, N=21		
Key Question 4. Are there subgroups based on demographics (age, racial groups, gender), other medications, or co-morbidities for which there are inter-class differences between DRI, ACE-I and AIIRA drugs			
HEART FAILURE AND CARDIOVASCULAR DISEASE			
Losartan vs. captopril (monotherapy)	Heart failure: ELITE and ELITE II Acute MI with HF or new Q-wave anterior wall MI: OPTIMAAL 3 trials N=9351	NA Study quality: fair 2, good 1	Overall summary Only 8 of 14 studies reported any data on population subgroups. There was NSD between AIIRAs and ARBs for subgroups based on age, ejection fraction, NYHA functional class (7 studies). Among patients on prior B-blocker therapy, more of the primary composite outcome occurred with losartan than with captopril.
Losartan vs. enalapril (monotherapy and combination therapy)	Heart failure Monotherapy: 3 trials (+ 2 poor quality), combination therapy: 1 trial N=302 (excluding poor quality studies)	NA Study quality: fair 2, fair-poor 1 (poor 2)	Specific comparisons Losartan vs. captopril: Among patients on prior B-blocker therapy, more events occurred with losartan than with captopril for the composite outcomes of all-cause mortality and hospital admissions ($P=0.024$) and for heart-failure-related mortality and admissions ($P=0.015$). NSD for primary outcome of all-cause mortality ($P>0.05$) (ELITE II). NSD for groups based on age, ejection fraction, NYHA functional class (3 studies). Losartan vs. enalapril: No significant interactions between treatment and subgroups based on age, sex, and NYHA functional class (2 studies). Telmisartan vs. ramipril vs. combination: For the primary composite outcome, results were similar between ramipril and telmisartan and between ramipril and combination therapy for subgroups based on cardiovascular disease, systolic blood pressure, diabetes, age, and sex. Valsartan vs. captopril vs. combination: Subgroups based on age, race (African-American vs. white) sex, diabetes, prior MI, heart failure, LVED, or prior ACE-I use did not produce significant differences in treatment effects. African Americans developed angioedema more than whites (2.1% vs. 1.2%, $P=0.2$). Valsartan vs. enalapril: Age, sex, pre-randomization B-blocker use, NYHA class, and
Telmisartan vs. ramipril vs. combination	Vascular disease or diabetes with end-organ damage but without symptomatic heart failure 1 trial (ONTARGET) N=25620	NA Study quality: good	
Valsartan vs. captopril vs. combination	Recent, acute MI complicated by HF or evidence of LVSD 1 trial (VALIANT) N=14703	NA Study quality: good	
Valsartan vs. enalapril (monotherapy)	Heart failure 1 trial (HEAVEN) N=141	NA Study quality: fair	

Comparison	Number of trials, N	Strength of the evidence (when NA, quality of individual studies) ^b	Conclusion
			etiology of HF produced no significant difference between the 2 groups in quality of life and dyspnea-fatigue index.
HYPERTENSION			
Eprosartan vs. enalapril	1 trial, N=529	NA (Fair)	Rate of cough was significantly lower for eprosartan vs. enalapril regardless of age (above or below 65 years) or Black race.
NONDIABETIC PROTEINURIA AND CHRONIC KIDNEY DISEASE (CKD)			
Losartan/enalapril	1 trial, N=40	NA, Fair	Overall summary: Only 6 of a total of 22 trials comparing monotherapy ACEI vs. AIIRA, combination therapy ACEI with AIIRA, or both conducted subgroup analyses. Two trials, losartan/enalapril and valsartan vs. lisinopril did not examine outcomes of interest within subgroup analyses. Only 2 trials examined the same outcomes, and each used different ACEI and AIIRA agents. The limited number of subgroups, different outcomes examined, and different drug comparisons used limits the generalizability and utility of these results.
Losartan/benazepril	1 trial, N=30	NA, Fair	
Valsartan vs. lisinopril	1 trial, N=37	NA, Fair	Losartan/benazepril conducted a subgroup analysis of participants with > 2 grams/day vs. <2 grams/day to examine antiproteinuric response to losartan vs. benazepril and Combination vs. monotherapy based on level of proteinuria. Those with >2 grams/day proteinuria had significantly greater reduction in proteinuria regardless of therapy.
Valsartan/ramipril	1 trial, N=18	NA, Fair	Two trials, irbesartan/ramipril and valsartan/ramipril examined differences in proteinuria reduction by CKD etiology (diabetic vs. non-diabetic CKD). There was no difference in proteinuric response for mono vs. mono therapy in 1 trial, and no difference for combination vs. mono therapy in either trial based on CKD etiology.
Candesartan with ramipril vs. ramipril	1 trial, N=43	NA, Fair	Candesartan/ramipril examined differences in proteinuria reduction by CKD etiology (IgA disease vs. diabetic nephropathy).
Irbesartan with ramipril vs. ramipril	1 trial, N=41	NA, Fair	Combination therapy resulted in significantly greater proteinuria reduction for IgA patients, but there was no significant difference in proteinuria reduction with combination therapy for those with diabetic nephropathy.
DIABETIC NEPHROPATHY			
Aliskiren plus losartan vs. losartan monotherapy	1 trial, N=599	NA, Fair	Dual therapy with aliskiren and losartan resulted in a greater reduction in the albumin-to-creatinine ratio vs. losartan monotherapy regardless of sex, race or age.

Abbreviations: AE, adverse event; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; HF, heart failure; LVED, left ventricular end-diastolic dysfunction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; NA, not applicable; NSD, no significant difference; NYHA, New York Heart Association.

^a Information about studies which received a rating of “poor” was not included in this summary table, but can be found in the Evidence Tables.

^b We did not grade bodies of evidence in which only a single study was available. Therefore, “Strength of Evidence” grades are listed as “not applicable”.

^c Only those harms reported in 3 or more trials were summarized here. Information on additional outcomes reported in 2 or fewer trials are available in the Results section and in the Evidence Tables.

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see External Validity

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The U.S. Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers — do not know which participants are assigned to each study group.

Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

CI: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report was hypothetically repeated on a collection of 100 random samples of studies, the resulting 100 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention used under ordinary circumstances does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a “real-world” population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result under ideal conditions in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability).

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See External Validity.

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See Adverse Event

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I²: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I² suggest heterogeneity. I² is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as $(Q-(n-1))/Q$, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the internal validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (heart attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See Blinding

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything

that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combining data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is < 1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomisation when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term “safe”) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.
Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected. The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measureable attribute that varies over time or between individuals. Variables can be
Discrete: taking values from a finite set of possible values (e.g. race or ethnicity)

Ordinal: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)

Continuous: taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B: Search strategies

Database: Ovid MEDLINE(R) <1950 to February Week 4 2009>

Search Strategy:

-
- 1 (losartan or cozaar).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (6035)
 - 2 (telmisartan or micardis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (692)
 - 3 (candesartan or atacand).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1909)
 - 4 (eprosartan or teveten).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (290)
 - 5 (irbesartan or avapro).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (984)
 - 6 (olmesartan or benicar).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (422)
 - 7 (valsartan or diovan).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1387)
 - 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (10325)
 - 9 (benazepril or lotensin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (496)
 - 10 (captopril or capoten).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (11712)
 - 11 (cilazapril or inhibace).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (614)
 - 12 (enalapril or vasotec).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (6463)
 - 13 (fosinopril or monopril).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (479)
 - 14 (lisinopril or prinivil or zestril).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2055)
 - 15 (moexipril or univasc).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (80)
 - 16 (quinapril or accupril).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (739)
 - 17 (ramipril or altace).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1820)
 - 18 (perindopril or aceon or coversyl).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1449)
 - 19 (trandolapril or mavik).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (586)
 - 20 11 or 9 or 17 or 12 or 15 or 14 or 18 or 19 or 10 or 13 or 16 (23267)
 - 21 8 and 20 (2077)
 - 22 limit 21 to (english language and humans) (964)

- 23 limit 22 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial or "review") (729)
 - 24 observational stud\$.mp. (18637)
 - 25 exp Cohort Studies/ or cohort.mp. (739805)
 - 26 exp Retrospective Studies/ or retrospective\$.mp. (366520)
 - 27 systematic review.mp. (13769)
 - 28 27 or 25 or 24 or 26 (1037318)
 - 29 22 and 28 (152)
 - 30 23 or 29 (751)
 - 31 from 30 keep 1-712 (712)
 - 32 from 31 keep 1-712 (712)
-

Database: Ovid MEDLINE(R) <1996 to February Week 4 2009>
 Search Strategy:

- 1 aliskiren.mp. (219)
 - 2 tekturna.mp. (7)
 - 3 rasilez.mp. (4)
 - 4 1 or 3 or 2 (219)
 - 5 limit 4 to (english language and humans) (181)
 - 6 limit 5 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or multicenter study or randomized controlled trial) (44)
 - 7 exp Case-Control Studies/ (309393)
 - 8 exp Cohort Studies/ (435651)
 - 9 systematic review.mp. (13343)
 - 10 8 or 7 or 9 (687251)
 - 11 4 and 10 (5)
 - 12 6 or 11 (48)
 - 13 from 12 keep 1-48 (48)
-

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2009>
 Search Strategy:

- 1 (losartan or cozaar).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (965)
- 2 (telmisartan or micardis).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (199)
- 3 (candesartan or atacand).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (418)
- 4 (eprosartan or teveten).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (84)
- 5 (irbesartan or avapro).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (271)

- 6 (olmesartan or benicar).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (50)
- 7 (valsartan or diovan).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (372)
- 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2139)
- 9 (benazepril or lotensin).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (204)
- 10 (captopril or capoten).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2017)
- 11 (cilazapril or inhibace).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (226)
- 12 (enalapril or vasotec).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2150)
- 13 (fosinopril or monopril).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (183)
- 14 (lisinopril or prinivil or zestril).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (720)
- 15 (moexipril or univasc).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (33)
- 16 (quinapril or accupril).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (258)
- 17 (ramipril or altace).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (544)
- 18 (perindopril or aceon or coversyl).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (461)
- 19 (trandolapril or mavik).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (193)
- 20 11 or 9 or 17 or 12 or 15 or 14 or 18 or 19 or 10 or 13 or 16 (6213)
- 21 8 and 20 (604)
- 22 limit 21 to (clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or randomized controlled trial) (422)
- 23 observational.mp. (1660)
- 24 retrospective.mp. (5067)
- 25 exp Cohort Studies/ or cohort.mp. (77012)
- 26 exp Case-Control Studies/ (5306)
- 27 systematic review.mp. (200)
- 28 27 or 25 or 24 or 26 or 23 (82556)
- 29 28 and 21 (101)
- 30 22 or 29 (424)
- 31 from 30 keep 1-424 (424)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2009>
Search Strategy:

- 1 aliskiren.mp. (31)

- 2 tekturna.mp. (0)
- 3 rasilez.mp. (0)
- 4 1 or 3 or 2 (31)
- 5 limit 4 to (english language and humans) [Limit not valid; records were retained] (31)
- 6 from 5 keep 1-31 (31)

 Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2009>
 Search Strategy:

- 1 (losartan or cozaar).mp. [mp=title, abstract, full text, keywords, caption text] (8)
- 2 (telmisartan or micardis).mp. [mp=title, abstract, full text, keywords, caption text] (7)
- 3 (candesartan or atacand).mp. [mp=title, abstract, full text, keywords, caption text] (9)
- 4 (eprosartan or teveten).mp. [mp=title, abstract, full text, keywords, caption text] (6)
- 5 (irbesartan or avapro).mp. [mp=title, abstract, full text, keywords, caption text] (9)
- 6 (olmesartan or benicar).mp. [mp=title, abstract, full text, keywords, caption text] (4)
- 7 (valsartan or diovan).mp. [mp=title, abstract, full text, keywords, caption text] (8)
- 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (16)
- 9 (benazepril or lotensin).mp. [mp=title, abstract, full text, keywords, caption text] (5)
- 10 (captopril or capoten).mp. [mp=title, abstract, full text, keywords, caption text] (27)
- 11 (cilazapril or inhibace).mp. [mp=title, abstract, full text, keywords, caption text] (9)
- 12 (enalapril or vasotec).mp. [mp=title, abstract, full text, keywords, caption text] (20)
- 13 (fosinopril or monopril).mp. [mp=title, abstract, full text, keywords, caption text] (11)
- 14 (lisinopril or prinivil or zestril).mp. [mp=title, abstract, full text, keywords, caption text] (12)
- 15 (moexipril or univasc).mp. [mp=title, abstract, full text, keywords, caption text] (7)
- 16 (quinapril or accupril).mp. [mp=title, abstract, full text, keywords, caption text] (9)
- 17 (ramipril or altace).mp. [mp=title, abstract, full text, keywords, caption text] (20)
- 18 (perindopril or aceon or coversyl).mp. [mp=title, abstract, full text, keywords, caption text] (15)
- 19 (trandolapril or mavik).mp. [mp=title, abstract, full text, keywords, caption text] (7)
- 20 11 or 9 or 17 or 12 or 15 or 14 or 18 or 19 or 10 or 13 or 16 (41)
- 21 8 and 20 (9)
- 22 from 21 keep 1-9 (9)

 Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2009>
 Search Strategy:

- 1 aliskiren.mp. (2)
- 2 tekturna.mp. (1)
- 3 rasilez.mp. (1)
- 4 1 or 3 or 2 (2)
- 5 from 4 keep 1-2 (2)

Appendix C. Methods used to assess quality of studies

Study quality was objectively assessed using predetermined criteria for internal validity, which were based on a combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination^{1,2} criteria.

All included studies, regardless of design, were assessed for quality and assigned a rating of “good,” “fair,” or “poor”. Studies that have a fatal flaw were rated poor quality. A fatal flaw was the failure to meet combinations of criteria that may be related to indicate the presence of bias. An example would be inadequate procedures for allocation concealment combined with important differences between groups in prognostic factors at baseline and following randomization. Studies that meet all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category was broad, studies with this rating varied in their strengths and weaknesses: The results of some fair-quality studies were *likely* to be valid, while others were only *possibly* valid. A poor-quality trial was not valid; the results were at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Criteria for assessing applicability (external validity) are also listed, although they were not used to determine study quality.

Systematic Reviews

1. Does the systematic review report a clear review question and clearly state inclusion and exclusion criteria for primary studies?

A good-quality review focuses on a well-defined question or set of questions, which ideally refer to the inclusion/exclusion criteria by which decisions are made about whether to include or exclude primary studies. These criteria would relate to the 4 components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. A good-quality review also includes details about the process of decision-making, that is, how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to find all relevant research?

If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, date restrictions, and language restrictions are presented. In addition, descriptions of hand-searches, attempts to identify unpublished material, and any contact with authors, industry, or research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE is searched for a systematic review about health education, then it is unlikely that all relevant studies will be located.

3. Is the validity of included studies adequately assessed?

If the review systematically assesses the quality of primary studies, it should include an explanation of the basis for determining quality (for example, method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis) and the process by which assessment is carried out (that is, how many reviewers are involved, whether the assessment is independent, and how discrepancies between reviewers are resolved). Authors

may have used either a published checklist or scale or one that they designed specifically for their review.

4. Is sufficient detail of the individual studies presented?

The review should show that the included studies are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. It is usually considered sufficient if a paper includes a table giving information on the design and results of individual studies or includes a narrative description of the studies. If relevant, the tables or text should include information on study design, sample size for each study group, patient characteristics, interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, according to sample size or according to inverse of the variance) so that studies that are thought to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?

Adequate approaches to sequence generation:

Computer-generated random numbers

Random numbers tables

Inferior approaches to sequence generation:

Use of alternation, case record number, birth date, or day of week

Not reported

2. Was the treatment allocation concealed?

Adequate approaches to concealment of randomization:

Centralized or pharmacy-controlled randomization

Serially-numbered identical containers

On-site computer based system with a randomization sequence that is not readable until allocation

Inferior approaches to concealment of randomization:

Use of alternation, case record number, birth date, or day of week

Open random numbers lists

Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to follow-up or overall high loss to follow-up? (Study should give number for each group.)

Nonrandomized studies

Assessment of Internal Validity

1. Was the selection of patients for inclusion unbiased? (Was any group of patients systematically excluded?)
2. Was there important differential loss to follow-up or overall high loss to follow-up? (Numbers should be given for each group.)
3. Were the events investigated specified and defined?
4. Was there a clear description of the techniques used to identify the events?
5. Was there unbiased and accurate ascertainment of events (that is, by independent ascertainers using a validated ascertainment technique)?
6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
7. Was the duration of follow-up reasonable for investigated events?

References

1. Center for Reviews and Dissemination, University of York, 2001. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. *CRD Report Number 4 (2nd edition)*..
2. Harris RP, Helfand M, Woolf SH. Current methods of the US Preventive Services Task Force: a review of the process. . *American Journal of Preventive Medicine*. 2001;20(3 Suppl):21-35.

Appendix D. Excluded trials

2=Wrong population, 3=wrong intervention, 4=wrong population, 5=wrong publication type, 6=wrong study design

Excluded trials	Exclusion code
<i>Head-to-head trials</i>	
Acbay O. Effects of low-dose losartan treatment on persistent microalbuminuria in normotensive type 1 diabetic subjects. <i>Journal of Endocrinological Investigation</i> . Sep 2001;24(8):608-611.	4
Aguilar D, Solomon SD, Kober L, et al. Newly diagnosed and previously known diabetes mellitus and 1-year outcomes of acute myocardial infarction: the VALsartan In Acute myocardial infarction (VALIANT) trial. <i>Circulation</i> . Sep 21 2004;110(12):1572-1578.	6
Alcocer L, Fernandez-Bonetti P, Campos E, Dominguez-Henkel R, de la Fuente JJ, Segovia-Ayala C. 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. <i>International Journal of Clinical Practice</i> . Dec 2004;Supplement.(145):23-28.	2
Altıparmak MR, Trablus S, Apaydin S, et al. Is losartan as effective as enalapril on posttransplant persistent proteinuria? <i>Transplantation Proceedings</i> . Nov-Dec 2001;33(7-8):3368-3369.	4
Anan F, Takahashi N, Ooie T, et al. Effects of valsartan and perindopril combination therapy on left ventricular hypertrophy and aortic arterial stiffness in patients with essential hypertension. <i>European Journal of Clinical Pharmacology</i> . Jul 2005;61(5-6):353-359.	2
Atmaca A, Gedik O. Effects of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and their combination on microalbuminuria in normotensive patients with type 2 diabetes. <i>Advances in Therapy</i> . Jul-Aug 2006;23(4):615-622.	4
Belonje AMS, Westenbrink BD, Voors AA, et al. Erythropoietin levels in heart failure after an acute myocardial infarction: determinants, prognostic value, and the effects of captopril versus losartan. <i>American Heart Journal</i> . Jan 2009;157(1):91-96.	2
Bogale N, Orn S, James M, et al. Usefulness of either or both left and right bundle branch block at baseline or during follow-up for predicting death in patients following acute myocardial infarction. <i>American Journal of Cardiology</i> . Mar 1 2007;99(5):647-650.	6

Excluded trials	Exclusion code
Bohm M, Baumhakel M, Probstfield JL, et al. Sexual function, satisfaction, and association of erectile dysfunction with cardiovascular disease and risk factors in cardiovascular high-risk patients: substudy of the ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNT Study in ACE-INtolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND). <i>American Heart Journal</i> . Jul 2007;154(1):94-101.	6
Campo C, Segura J, Fernandez ML, Guerrero L, Christiansen H, Ruilope LM. A prospective comparison of four antihypertensive agents in daily clinical practice. <i>Journal of Clinical Hypertension</i> . May-Jun 2001;3(3):139-144.	2
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. <i>International Journal of Clinical Practice</i> . Dec 1999;53(8):584-592.	2
Demers C, McKelvie RS, Negassa A, Yusuf S, Investigators RPS. Reliability, validity, and responsiveness of the six-minute walk test in patients with heart failure. <i>American Heart Journal</i> . Oct 2001;142(4):698-703.	2
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. <i>American Journal of Nephrology</i> . Sep-Oct 2003;23(5):300-306.	4
Elliott WJ. Double-blind comparison of eprosartan and enalapril on cough and blood pressure in unselected hypertensive patients. Eprosartan Study Group. <i>Journal of Human Hypertension</i> . Jun 1999;13(6):413-417.	2
Erley CM, Bader B, Scheu M, Wolf S, Braun N, Risler T. Renal hemodynamics in essential hypertensives treated with losartan. <i>Clinical Nephrology</i> . Jan 1995;43 Suppl 1:S8-11.	2
Fried LF, Duckworth W, Zhang JH, et al. Design of combination angiotensin receptor blocker and angiotensin-converting enzyme inhibitor for treatment of diabetic nephropathy (VA NEPHRON-D). <i>Clinical Journal of The American Society of Nephrology: CJASN</i> . Feb 2009;4(2):361-368.	6
Gang Y, Ono T, Hnatkova K, et al. QT dispersion has no prognostic value in patients with symptomatic heart failure: an ELITE II substudy. <i>Pacing & Clinical Electrophysiology</i> . Jan 2003;26(1 Pt 2):394-400.	2

Excluded trials	Exclusion code
Gansevoort RT, de Zeeuw D, de Jong PE. Is the antiproteinuric effect of ACE inhibition mediated by interference in the renin-angiotensin system? <i>Kidney International</i> . Mar 1994;45(3):861-867.	6
Hetzel GR, Hermsen D, Hohlfeld T, et al. Effects of candesartan and perindopril on renal function, TGF-beta1 plasma levels and excretion of prostaglandins in stable renal allograft recipients.[see comment]. <i>Clinical Nephrology</i> . Apr 2002;57(4):296-302.	4
Hortal L, Fernandez A, Vega N, et al. Losartan versus ramipril in the treatment of postrenal transplant erythrocytosis. <i>Transplantation Proceedings</i> . Aug 1998;30(5):2127-2128.	5
Kincaid-Smith P, Fairley K, Packham D. Randomized controlled crossover study of the effect on proteinuria and blood pressure of adding an angiotensin II receptor antagonist to an angiotensin converting enzyme inhibitor in normotensive patients with chronic renal disease and proteinuria.[erratum appears in <i>Nephrol Dial Transplant</i> 2002 Jun;17(6):1153]. <i>Nephrology Dialysis Transplantation</i> . Apr 2002;17(4):597-601.	3
Krimholtz MJ, Karalliedde J, Thomas S, Bilous R, Viberti G. Targeting albumin excretion rate in the treatment of the hypertensive diabetic patient with renal disease. <i>Journal of the American Society of Nephrology</i> . Mar 2005;16 Suppl 1:S42-47.	6
Kum LC, Yip GW, Lee PW, et al. Comparison of angiotensin-converting enzyme inhibitor alone and in combination with irbesartan for the treatment of heart failure. <i>International Journal of Cardiology</i> . Mar 28 2008;125(1):16-21.	6
Lacourciere Y. The incidence of cough: a comparison of lisinopril, placebo and telmisartan, a novel angiotensin II antagonist. <i>Telmisartan Cough Study Group</i> . <i>International Journal of Clinical Practice</i> . Mar 1999;53(2):99-103.	2
Lacourciere Y, Brunner H, Irwin R, et al. Effects of modulators of the renin-angiotensin-aldosterone system on cough. <i>Losartan Cough Study Group</i> . <i>Journal of Hypertension</i> . Dec 1994;12(12):1387-1393.	2
Lacourciere Y, Lefebvre J, Nakhle G, Faison EP, Snavely DB, Nelson EB. Association between cough and angiotensin converting enzyme inhibitors versus angiotensin II antagonists: the design of a prospective, controlled study. <i>Journal of Hypertension - Supplement</i> . Jul 1994;12(2):S49-53.	5

Excluded trials	Exclusion code
Larochelle P, Flack JM, Marbury TC, Sareli P, Krieger EM, Reeves RA. Effects and tolerability of irbesartan versus enalapril in patients with severe hypertension. Irbesartan Multicenter Investigators. American Journal of Cardiology. Dec 15 1997;80(12):1613-1615.	2
Liebson PR, Amsterdam EA. Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET): implications for reduced cardiovascular risk. Preventive Cardiology. 2009;12(1):43-50.	4
Matsuda H, Hayashi K, Saruta T. Distinct time courses of renal protective action of angiotensin receptor antagonists and ACE inhibitors in chronic renal disease. Journal of Human Hypertension. Apr 2003;17(4):271-276.	6
Mauer M, Zinman B, Gardiner R, et al. ACE-I and ARBs in early diabetic nephropathy. Journal of the Renin-Angiotensin-Aldosterone System. Dec 2002;3(4):262-269.	4
McKelvie RS, Rouleau J-L, White M, et al. Comparative impact of enalapril, candesartan or metoprolol alone or in combination on ventricular remodelling in patients with congestive heart failure.[see comment]. European Heart Journal. Oct 2003;24(19):1727-1734.	2
Mimran A, Ruilope L, Kerwin L, et al. A randomised, double-blind comparison of the angiotensin II receptor antagonist, irbesartan, with the full dose range of enalapril for the treatment of mild-to-moderate hypertension. Journal of Human Hypertension. Mar 1998;12(3):203-208.	2
Nielsen S, Dollerup J, Nielsen B, Jensen HA, Mogensen CE. Losartan reduces albuminuria in patients with essential hypertension. An enalapril controlled 3 months study. Nephrology Dialysis Transplantation. 1997;12 Suppl 2:19-23.	2
Paster RZ, Snavely DB, Sweet AR, et al. Use of losartan in the treatment of hypertensive patients with a history of cough induced by angiotensin-converting enzyme inhibitors. Clinical Therapeutics. Sep-Oct 1998;20(5):978-989.	2
Ramsay LE, Yeo WW. ACE inhibitors, angiotensin II antagonists and cough. The Losartan Cough Study Group. Journal of Human Hypertension. Nov 1995;9 Suppl 5:S51-54.	2
Ramsay LE, Yeo WW, Losartan Cough Study G. Double-blind comparison of losartan, lisinopril and hydrochlorothiazide in hypertensive patients with a previous angiotensin converting enzyme inhibitor-associated cough. Journal of Hypertension - Supplement. Jul 1995;13(1):S73-76.	2

Excluded trials	Exclusion code
Rossing K, Jacobsen P, Pietraszek L, Parving H-H. Renoprotective effects of adding angiotensin II receptor blocker to maximal recommended doses of ACE inhibitor in diabetic nephropathy: a randomized double-blind crossover trial. <i>Diabetes Care</i> . Aug 2003;26(8):2268-2274.	3
Russo D, Pisani A, Balletta MM, et al. Additive antiproteinuric effect of converting enzyme inhibitor and losartan in normotensive patients with IgA nephropathy. <i>American Journal of Kidney Diseases</i> . May 1999;33(5):851-856.	6
Sato A, Tabata M, Hayashi K, Saruta T. Effects of the angiotensin II type 1 receptor antagonist candesartan, compared with angiotensin-converting enzyme inhibitors, on the urinary excretion of albumin and type IV collagen in patients with diabetic nephropathy. <i>Clinical & Experimental Nephrology</i> . Sep 2003;7(3):215-220.	6
Schulz E, Bech JN, Pedersen EB, Muller GA. A randomized, double-blind, parallel study on the safety and antihypertensive efficacy of losartan compared to captopril in patients with mild to moderate hypertension and impaired renal function. <i>Nephrology Dialysis Transplantation</i> . 1999;14 Suppl 4:27-28.	5
Shoda J, Kanno Y, Suzuki H. A five-year comparison of the renal protective effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with non-diabetic nephropathy.[see comment]. <i>Internal Medicine</i> . 2006;45(4):193-198.	6
Solomon SD, Appelbaum E, Manning WJ, et al. Effect of the direct Renin inhibitor aliskiren, the Angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. <i>Circulation</i> . Feb 3 2009;119(4):530-537.	2
Suzuki H, Kusuyama T, Omori Y, et al. Inhibitory effect of candesartan cilexetil on left ventricular remodeling after myocardial infarction. <i>International Heart Journal</i> . Sep 2006;47(5):715-725.	3
Trojjan TH, Jackson EA. Is losartan superior to captopril in reducing all-cause mortality in elderly patients with symptomatic heart failure? <i>Journal of Family Practice</i> . Aug 2000;49(8):759-760.	4
Tylicki L, Renke M, Rutkowski P, et al. Dual blockade of the renin-angiotensin-aldosterone system with high-dose angiotensin-converting enzyme inhibitor for nephroprotection: an open, controlled, randomized study. <i>Scandinavian Journal of Urology & Nephrology</i> . 2008;42(4):381-388.	6

Excluded trials	Exclusion code
Woo KT, Lau YK, Wong KS, Chiang GS. ACEI/ATRA therapy decreases proteinuria by improving glomerular permselectivity in IgA nephritis. <i>Kidney International</i> . Dec 2000;58(6):2485-2491.	6
Yin Y, Dalal D, Liu Z, et al. Prospective randomized study comparing amiodarone vs. amiodarone plus losartan vs. amiodarone plus perindopril for the prevention of atrial fibrillation recurrence in patients with lone paroxysmal atrial fibrillation.[see comment]. <i>European Heart Journal</i> . Aug 2006;27(15):1841-1846.	4
Active-control trials	
Benz J, Oshrain C, Henry D, Avery C, Chiang YT, Gatlin M. Valsartan, a new angiotensin II receptor antagonist: a double-blind study comparing the incidence of cough with lisinopril and hydrochlorothiazide. <i>Journal of Clinical Pharmacology</i> . Feb 1997;37(2):101-107.	2
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.[see comment][summary for patients in <i>Ann Intern Med</i> . 2003 Apr 1;138(7):I43; PMID: 12667050]. <i>Annals of Internal Medicine</i> . Apr 1 2003;138(7):542-549.	6
Hasford J, Bussmann WD, Delius W, Koepcke W, Lehmann K, Weber E. First dose hypotension with enalapril and prazosin in congestive heart failure. <i>International Journal of Cardiology</i> . Jun 1991;31(3):287-293.	6
Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes.[see comment]. <i>New England Journal of Medicine</i> . Sep 20 2001;345(12):851-860.	6
Rossing K, Christensen PK, Jensen BR, Parving H-H. Dual blockade of the renin-angiotensin system in diabetic nephropathy: a randomized double-blind crossover study.[see comment]. <i>Diabetes Care</i> . Jan 2002;25(1):95-100.	2
Placebo-controlled trials	
Anonymous. Safety and Efficacy of the Antihypertensive Drug Aliskiren in Patients with Hypertension, Type 2 Diabetes and Proteinuria. <i>ClinicalTrials.gov</i> , National Institutes of Health [http://www.clinicaltrials.gov]. 2005.	5

Excluded trials	Exclusion code
Blanchet M, Sheppard R, Racine N, et al. Effects of angiotensin-converting enzyme inhibitor plus irbesartan on maximal and submaximal exercise capacity and neurohumoral activation in patients with congestive heart failure. <i>American Heart Journal</i> . May 2005;149(5):938.e931-937.	6
Chrysant SG, Murray AV, Hoppe UC, et al. Long-term safety, tolerability and efficacy of aliskiren in combination with valsartan in patients with hypertension: a 6-month interim analysis. <i>Current Medical Research & Opinion</i> . Apr 2008;24(4):1039-1047.	6
Iodice C, Balletta MM, Minutolo R, et al. Maximal suppression of renin-angiotensin system in nonproliferative glomerulonephritis. <i>Kidney International</i> . Jun 2003;63(6):2214-2221.	6
Kim MJ, Song JH, Suh JH, Lee SW, Kim GA. Additive antiproteinuric effect of combination therapy with ACE inhibitor and angiotensin II receptor antagonist: differential short-term response between IgA nephropathy and diabetic nephropathy. <i>Yonsei Medical Journal</i> . Jun 30 2003;44(3):463-472.	6
Kostis JB, Shelton B, Gosselin G, et al. Adverse effects of enalapril in the Studies of Left Ventricular Dysfunction (SOLVD). SOLVD Investigators. <i>American Heart Journal</i> . Feb 1996;131(2):350-355.	6
McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial.[see comment]. <i>Lancet</i> . Sep 6 2003;362(9386):767-771.	3
Tan KC, Chow WS, Ai VH, Lam KS. Effects of angiotensin II receptor antagonist on endothelial vasomotor function and urinary albumin excretion in type 2 diabetic patients with microalbuminuria. <i>Diabetes/Metabolism Research Reviews</i> . Jan-Feb 2002;18(1):71-76.	6

Appendix E. Black box warnings for included drugs

Trade name	Active ingredient	Black box warnings	
Tekturna [®]	Aliskiren		
Lotensil [®]	Benazepril		
Capoten [®]	Captopril		
Vasotec [®]	Enalapril		
Monopril [®]	Fosinopril		
Prinivil [®]	Lisinopril		
Zestril [®]	Lisinopril		
Univasc [®]	Moexipril	When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, drug should be discontinued as soon as possible.	
Accupril [®]	Quinapril		
Altace [®]	Ramipril		
Aceon [®]	Perindopril		
Mavik [®]	Trandolapril		
Cozaar [®]	Losartan		
Micardis [®]	Telmisartan		
Atacand [®]	Candesartan		
Teveten [®]	Eprosartan		
Avapro [®]	Irbesartan		
Benicar [®]	Olmesartan		
Rasilez [®]	Aliskiren		Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, Rasilez should be discontinued as soon as possible.
Inhibace [®]	Cilazapril		When used in pregnancy, these drugs can cause injury or even death of the developing fetus. When pregnancy is detected, Inhibace should be discontinued as soon as possible.
Coversyl [®]	Perindopril		
Diovan [®]	Valsartan		