



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

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Based on the DERP report of December 2009

Produced by:
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Health Resources Commission

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative and two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee for this review consisted of three Physicians, a Nurse Practitioner, and two pharmacists. All meetings were held in public with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon

Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC's report, "Direct Renin Inhibitors, Angiotensin Converting Enzyme Inhibitors, and Angiotensin II Receptor Blockers", December 2009, was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately twice per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report, "*Direct Renin Inhibitors, Angiotensin Converting Enzyme Inhibitors, and Angiotensin II Receptor Blockers*" is available via the Drug Effectiveness review Project website:

<http://derp.ohsu.edu/about/final-products.cfm>

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Health Resources Commission website:

<http://www.oregon.gov/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

Health Resources Commission

– “Clinical outcomes are the most important indicators of comparative effectiveness”

– “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Clinical Overview

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 (see 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	Black Box Warnings?
Direct Renin Inhibitor (DRI)					
Aliskiren Oral Tablet	Tekturna®	EQ 150-300mg base	150-300 mg in 1 dose	1) Hypertension	Y
Angiotensin converting enzyme inhibitor (ACE-I)					
Benazepril Oral Tablet	Lotensin®	5-40 mg	10-80 mg in 1 or 2 doses	1) Hypertension	Y
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	Y
Enalapril Oral Tablet	Vasotec®	2.5-20 mg	2.5-40 mg in 1 or 2 doses	1) Hypertension 2) Congestive heart failure	Y
Fosinopril Oral Tablet	Monopril®	10-40 mg	10-80 mg in 1 or 2 doses	1) Hypertension 2) Heart failure	Y
Lisinopril Oral Tablet	Prinivil®, Zestril®	2.5-40 mg	5-40 mg in 1 dose	1) Hypertension 2) Heart failure 3) Acute myocardial infarction	Y

Moexipril Oral Tablet	Univasc®	7.5-15 mg	7.5-30 mg 1 or 2 doses	1) Hypertension	Y
Perindopril Oral Tablet	Aceon®	2-8 mg	4-8 mg in 1 or 2 doses	1) Stable coronary artery disease 2) Hypertension	Y
Quinapril Oral Tablet	Accupril®	5-40 mg	5-80 mg in 1 or 2 doses	1) Hypertension 2) Congestive heart failure	Y
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 myocardial infarction	Y
Trandolapril Oral Tablet	Mavik®	1-4 mg	1-8 mg in 1 or 2 doses	1) Hypertension 2) Heart failure post myocardial infarction, or left ventricular dysfunction post myocardial infarction	Y
Angiotensin II receptor blocker (AIIRA)					
Candesartan Oral tablet	Atacand®	4-32 mg	8-32 mg in 1 dose	1) Hypertension 2) Heart failure	Y
Eprosartan Oral Tablet	Teveten®	EQ 400-600 mg base	400-800 mg in 1 or 2 doses	1) Hypertension	Y
Irbesartan Oral Tablet	Avapro®	75-300 mg	150-300 mg in 1 dose	1) Hypertension 2) Nephropathy in type 2 diabetes patients	Y
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	Y
Olmesartan Oral Tablet	Benicar®	5-40 mg	20-40 mg in 1 dose	1) Hypertension	Y
Telmisartan Oral Tablet	Micardis®	20-80 mg	40-80 mg in 1 dose	1) Hypertension	Y
Valsartan Oral Tablet	Diovan®	40-320 mg	80-320 mg in 1 dose	1) Hypertension 2) Heart failure 3) Post myocardial infarction	Y

a: Obtained from the *Medical Letter*.

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of

evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

The subcommittee's task was to evaluate

Scope and Key Questions

The EPC 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). The EPC attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, they 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, they 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.

The goal of this report is to compare the effectiveness and harms between aliskiren and placebo and between AIIIRAs and ACEIs in the treatment of diagnosed coronary heart disease, hypertension, left ventricular dysfunction, heart failure, nondiabetic chronic kidney disease, or diabetic nephropathy.

Draft Key questions were posted on the DERP website and a group of clinicians specializing in nephrology and hypertension were consulted for clinical insight into the proposed key questions. Revision into the final Key Questions 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 of interest to participating DERP organizations. These organizations approved the following key questions to guide the review for this report:

KQ1. 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?

- a. When used as monotherapy?
- b. When used in combination with angiotensin converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (AIIRA) drugs?

KQ2. 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?

- a. When used as monotherapy?
- b. When used in combination with one another?

KQ3. 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?

KQ4. 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?

Conclusions:

Limitations of the Evidence

1. 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.
2. Few studies were available for many ACE-I vs. ARB comparisons.
3. Evidence regarding Aliskirin was limited to two studies.
4. 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.

Conclusions:

1. There are no clinically significant differences among ACE-Is as monotherapy, ARBs as monotherapy, or ACE-I + ARB combination therapy.
2. Combination therapy with an ACE-I and an ARB produces a reduction in proteinuria in nondiabetic proteinuria or chronic kidney disease but produced no clinically significant difference in other measures of renal function.
3. Rates of cough were lower with ARBs than ACE-Is however overall rates of withdrawal were the same.
4. There were no included studies that evaluated comparative effectiveness/ efficacy and harms between aliskirin and placebo as monotherapy or for combination therapy with ACE-I and ARB.

5. There was no significant difference found between AIIRAs and ARBs for subgroups based on age, ejection fraction, or NYHA functional class (7 studies) for patients with heart failure or cardiovascular disease.

Supporting Evidence:

Key Question 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?

- a. When used as monotherapy?
- b. When used in combination with angiotensin converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (AIIRA) drugs?

Coronary Heart Disease, Heart Failure, and Left Ventricular Dysfunction

A total of 14 randomized controlled trials (in 27 publications) compared ACE-Is to AIIRAs among patients with heart disease, including heart failure, left ventricular dysfunction, or coronary heart disease. 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 ONTARGET ³¹ more than 25 000. A single trial compared aliskiren to placebo in patients with heart failure and hypertension.³⁸

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 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.

Key Question 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?

- a. When used as monotherapy?
- b. When used in combination with one another?

Coronary Heart Disease, Heart Failure, and Left Ventricular Dysfunction

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^{33, 39} 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.

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 ELITE 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 Euroqol-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 OPTIMAAL 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; $P=0.032$).

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

Five small trials compared losartan with enalapril, all in populations with stable heart failure, two were rated poor quality. Of the three remaining studies follow up was short term (8-12 weeks). Two of these studies involved patients stabilized on an ACE-I,^{26, 32} while other included only subjects with no recent use of ACE-Is or AIIRAs³⁰. The largest study was 166 patients.²⁶ 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.

Exercise capacity improved with both losartan and enalapril, with no significant difference between monotherapy treatment groups.^{26, 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.

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

The REPLACE (the replacement of angiotensin converting enzyme inhibition) trial ²⁸ 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.

Telmisartan compared with ramipril (monotherapy and combination therapy)

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).

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.

Valsartan compared with captopril (monotherapy and combination therapy)

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).

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.

Hypertension

Monotherapies

Losartan

Losartan compared with enalapril

Three trials of losartan compared with enalapril were rated fair quality.[56, 73, 76](#) 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 trial[56](#) 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.

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 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.

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.

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

Candesartan

Candesartan compared with enalapril

We included 2 fair quality trials that compared starting doses of candesartan 8 mg to enalapril 10 mg.^{66, 75} The trials ranged in duration from 2 months⁷⁵ to 6 months.⁶⁶ In one trial, the candesartan and enalapril dosages were doubled after 6 weeks if the diastolic blood pressure was at or above 90 mm Hg⁶⁶. In the second trial, there was the possibility to add hydrochlorothiazide 12.5 if diastolic blood pressure was above 105 mm Hg.⁷⁵

The 2 trials had 63%⁷⁵ and 100%,⁶⁶ respectively, of their participants that were female.

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}

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.

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

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.

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

Eprosartan

Eprosartan compared with enalapril

We included 3 fair-quality trials (reported in 7 publications) of eprosartan compared with enalapril in adults with hypertension. Duration of follow-up ranged from 6 weeks⁶⁷ to 6 months. Sample sizes ranged from 136 participants⁶⁷ to 529 participants. Two trials involved the comparison of eprosartan 300 mg to enalapril 20 mg. 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. The third trial exclusively enrolled participants aged over 65 years and had a mean age of 73 years.⁷⁰

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}

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.

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

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

We included 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.

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.

Nondiabetic (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}

One 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

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.

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.

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

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 AIIA 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.

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).

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. Participants included in this trial had specific types of glomerulonephritis including proliferative glomerulonephritis, membranous glomerulonephritis, and focal segmental glomerulosclerosis. 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 AIIA was noted (statistical analysis was not provided). There were no significant differences in blood pressure control between treatment arms.

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.

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.). 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.

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.

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.

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

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.

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

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.

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.

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.

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

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 ($P<0.05$).

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. 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. 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, $P=0.009$).

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. 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).

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.

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. 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.

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. 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

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

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. 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.

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.

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.

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.

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.

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.

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.

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 ($P=0.00009$).

Diabetic Nephropathy

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

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%).

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

We included 16 trials 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 and to quinapril in 1 trial. Telmisartan was compared with enalapril in the Diabetics Exposed to Telmisartan and enalapril (DETAIL) trial. Candesartan was compared with lisinopril in 1 trial and to ramipril in 1 trial. Irbesartan was compared with perindopril in 1 trial. Valsartan was compared with benazepril in 1 trial, to enalapril in 1 trial, and to captopril in 1 trial. Only 1 trial was rated good quality, 12 were rated fair quality, 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 centers 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%.

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

Losartan

Losartan compared with enalapril

Losartan was compared with enalapril in 5 trials (N=201) conducted in Canada,¹²⁸ Denmark,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 heterogeneous 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 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

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 (1 good, 5 fair, 2 poor quality) that compared the combination of an AIIRA and an ACE-I with either or both as monotherapy. The majority of trials ranged from 8 weeks to 16 weeks in duration. 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.

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 diabetics 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.

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

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 normoalbuminuria (70% compared with 67% or 83%). Attrition was 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.

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 $+44$).

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 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.

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. 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.

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). 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 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 (ml/min/1.73 m²) 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.

Key Question 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?

Coronary Heart Disease, Heart Failure, and Left Ventricular Dysfunction

Candesartan compared with enalapril (monotherapy and combination therapy) (n=1)
RESOLVD^{33, 39} 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.

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

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. Additionally, 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 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 ($P<0.001$). 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.

Losartan compared with enalapril (monotherapy and combination therapy)

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

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

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 ($P=0.30$).

Telmisartan compared with ramipril (monotherapy and combination therapy)

In the ONTARGET study 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.

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

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

Valsartan compared with captopril (monotherapy and combination therapy)

In the VALIANT trial the percentage of patients not taking the study medication at the end of the study was higher with combination therapy than with captopril alone ($P=0.007$). 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 ($P<0.05$).

Valsartan compared with enalapril (monotherapy)

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).³⁶

Hypertension

Monotherapies

Losartan

Losartan compared with enalapril

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}

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

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.

Candesartan

Candesartan compared with enalapril

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.

Candesartan compared with lisinopril and perindopril

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

Valsartan

Valsartan compared with benazepril, lisinopril, and ramipril

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

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.

Eprosartan

Eprosartan compared with enalapril

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. 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. Few participants withdrew due to cough, however, and the difference between eprosartan and enalapril was not significant in 2 trials.^{55, 58, 61, 67}

Telmisartan

Telmisartan compared with enalapril and ramipril

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.

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

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

There were no significant differences between groups for overall withdrawals in any of the trials.

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

Nondiabetic Chronic Kidney Disease

Losartan

Losartan compared with lisinopril

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).⁸⁹

Losartan compared with enalapril

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.^{92, 102, 103}

Losartan compared with 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%.

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

Information on harms and withdrawals not reported.

Losartan compared with perindopril

Information on harms and withdrawals not reported.

Candesartan

Candesartan compared with lisinopril

Only 1 withdrawal was reported for this study⁹⁰, 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.

Candesartan compared with perindopril and trandolapril

Information on harms and withdrawals not reported

Valsartan

Valsartan compared with lisinopril

Two participants were withdrawn from this study⁸³, 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

One study reported no withdrawals,⁸⁴ and the other study did not provide information on withdrawals.¹⁰⁵

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

One study reported 14 withdrawals, all of which were related to adverse events;⁹⁵ the remaining study reported 2 withdrawals, 1 of which was related to an adverse event.⁸⁵ 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 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

The included trial⁸⁶ 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

Monotherapy with ACE-I and AIIRA compared with combination therapy

Losartan

Losartan in combination with lisinopril

The included trial⁸⁹ 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

Each of the include trials reported 2 withdrawals. 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

Each included trial reported 6 withdrawals. 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 participant was withdrawn from the included study⁹⁰. 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

One included 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

Adverse events in the included study⁸⁵ 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

Authors reported 1 withdrawal from the included trial⁸⁶. 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 participant was withdrawn from the included study.¹⁰⁷ Harms and adverse events were not reported.

Candesartan and ramipril compared with ramipril alone

The two included trials reported 2 withdrawals.

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 withdrawal was reported in the included study¹⁰⁸. 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

The included trial reported 9 withdrawals¹¹⁰. 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

The included trial¹¹¹ 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%).

Diabetic Nephropathy

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

Incidence of overall withdrawals in the included study¹¹⁸ was similar for aliskiren (14%) compared with placebo (11%).

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.

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

Telmisartan

Telmisartan compared with enalapril

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 ¹²⁰⁻¹²².

Losartan

Losartan compared with enalapril

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

Information on harms was reported in 4 trials. 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

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

Combination therapy with losartan plus enalapril

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

Combination therapy with candesartan plus an ACE-I

Candesartan plus lisinopril

Overall rates of withdrawal were similar for combination therapy (27%) compared with candesartan (26%) and lisinopril (28%)¹³¹. 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%).

Candesartan plus ramipril

A total of 16% of participants did not complete the included trial¹³². Individual treatment group withdrawal rates were not provided separately. 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%).

Combination therapy with irbesartan plus enalapril

All participants completed the trial. 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).

Combination therapy with valsartan plus benazepril

Only 2 participants withdrew from the included trial¹²⁵ (11%), both due to adverse events and both during benazepril monotherapy. 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.

Serious Harms in Observational Studies: All Populations

We identified 14 studies with sample size ≥ 1000 patients that examined adverse events in either ACE-I 138-145 or AIIRAs.146-151 No studies examined aliskiren. Most studies were open-label, prospective, single-group cohort or post-marketing surveillance studies, while several were retrospective. 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

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, 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.

Angioedema and allergic reactions

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](#) cilapaparil,[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 colleagues[139](#) (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 coauthors[138](#) reported 3 cases of nonfatal thrombocytopenia with perindopril (N=47,351).

Adverse events in subpopulations

Few studies examined subgroups based on age or gender; no study examined racial/ethnic groups. Chalmers and colleagues[139](#) 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 gender 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 non-serious 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.

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?

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

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, gender, 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, gender, diabetes, Killip class, infarct location, prior myocardial infarction, heart failure, and thrombolytic or beta-blocker use.

Losartan compared with enalapril (monotherapy and combination therapy)

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

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

No data on subgroups were reported.

Telmisartan compared with ramipril (monotherapy and combination therapy)

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 gender.³¹

Valsartan compared with captopril (monotherapy and combination therapy)

In the main trial (VALIANT),¹³ subgroups based on age, gender, 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)

In the HEAVEN trial³⁶ Age (<65 years compared with ≥ 65 years), gender, 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.

Hypertension

Monotherapies

Losartan

Losartan compared with enalapril

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

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

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

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

Candesartan compared with lisinopril and perindopril

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

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

Results of subgroup analyses of incidence of cough in participants under (N=403) and over (N=125) 65 years of age ⁵³ 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, and similar results were found in both the older, younger and Black subgroups of participants.

Telmisartan

Telmisartan compared with enalapril and ramipril

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

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

Losartan

No subgroup information meeting inclusion criteria was found.

Candesartan

No subgroup information meeting inclusion criteria was found.

Valsartan

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.

Telmisartan

No subgroup information meeting inclusion criteria was found.

Irbesartan,

No subgroup information meeting inclusion criteria was found.

Monotherapy with ACE-I and AIIRA compared with combination therapy

Losartan in combination with benazepril

No subgroup information meeting inclusion criteria was found.

Candesartan in combination with lisinopril

No subgroup information meeting inclusion criteria was found.

Valsartan in combination with benazepril

No subgroup information meeting inclusion criteria was found.

Valsartan in combination with ramipril

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).

Irbesartan in combination with fosinopril

No subgroup information meeting inclusion criteria was found.

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

No subgroup information meeting inclusion criteria was found.

Candesartan and ramipril compared with ramipril alone

One study performed a subgroup analysis by type of chronic kidney disease.¹⁰⁹ The 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.

Irbesartan and ramipril compared with ramipril alone

No subgroup information meeting inclusion criteria was found.

ACE-I and AIIRA compared with AIIRA alone

Candesartan and benazepril compared with candesartan alone

No subgroup information meeting inclusion criteria was found.

Valsartan and benazepril compared with valsartan alone

No subgroup information meeting inclusion criteria was found.

Diabetic Nephropathy

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

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)¹¹⁸.

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

Telmisartan

Telmisartan compared with enalapril

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

Losartan

Losartan compared with enalapril

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

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

Combination therapy with losartan plus enalapril

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

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

Candesartan plus ramipril

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

Combination therapy with irbesartan plus enalapril

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

Combination therapy with valsartan plus benazepril

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