Drug Class Review
on
Angiotensin II Receptor Antagonists

Final Report Update 1

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Original Report Date: September 2004
A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Elaine Furmaga, PharmD
Peter Glassman, MBBS, MSc
Shannon Rhodes, MSPH
Marika Suttorp, MS
Walter Mojica, MD, MSPH
Produced by
Southern California Evidence-based Practice Center
RAND
1700 Main Street, PO Box 2138
Santa Monica, CA 90407
Paul Shekelle, co-Director

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date. Prior version of this report can be accessed at the DERP website.

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Suggested citation for this report

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Acknowledgements

Introduction

The angiotensin II receptor antagonists (AIIRAs, also referred to as ARBs or angiotensin receptor blockers) selectively inhibit angiotensin II from activating the angiotensin II type 1 receptor (AT_1). This action blocks vasoconstriction, sodium and water retention, activation of the sympathetic nervous system, constriction of the afferent and efferent arteriole in the kidney, and stimulation of vascular and myocardial fibrosis.[1]

The mechanism of action of the angiotensin II receptor antagonists differs from that of the angiotensin-converting enzyme inhibitors (ACEI) in that the ACEIs block the conversion of angiotensin I to angiotensin II. Since angiotensin II can be produced by other enzymes, its effects are not entirely blocked by ACEIs. In addition, the ACEIs interfere with the breakdown of bradykinin and substance P, which is thought to be the cause of some of their side effects, including cough and angioedema.

Like the ACEIs, the angiotensin II receptor antagonists are useful in the management of patients with hypertension (HTN), patients at high cardiovascular (CV) risk, patients with CV disease such as heart failure (HF) or myocardial infarction (MI) complicated by heart failure of left ventricular dysfunction (LVD), and patients with diabetes mellitus (DM) and renal disease. Whether the angiotensin II receptor antagonists are equivalent to the ACEIs in their renal and cardioprotective effects is being evaluated in clinical trials.

A summary of some of the recommendations from clinical practice guidelines and/or Associations or Committees on therapy with the angiotensin II receptor antagonists are included in Table 1.

Table 1. Guideline Recommendations on the Use of Angiotensin II Receptor Antagonists

Guideline or Association/ Committee	Condition	Recommendations
JNC 7* (2003)[2]	HTN	Thiazide-type diuretic as first-line therapy in most patients with HTN, alone or in combination with an ACEI, angiotensin II receptor antagonist, beta-adrenergic blocker, or calcium channel blocker. An agent from one of these classes may be considered as initial therapy if a thiazide cannot be used or there is a compelling indication for another class. It is also recommended that an angiotensin II receptor antagonist may be considered in patients with compelling indications such as HF, high coronary disease risk, DM, and chronic kidney disease
ACC/AHA** (2005)[3]	HF	An angiotensin II receptor antagonist approved for the treatment of HF is recommended in patients with HF who are unable to tolerate an ACEI. It is considered reasonable to use an angiotensin II receptor antagonist as an alternative to an ACEI in patients with mild to moderate HF, especially if already taking an angiotensin II receptor antagonist for another indication. An angiotensin II receptor antagonist may be considered in addition to conventional therapy in patients with persistent symptoms
ACC/AHA** (2005)[3]	Post-MI	An angiotensin II receptor antagonist is recommended in post-MI patients without HF that have a low left ventricular ejection fraction and who are unable to tolerate an ACEI

| ADA*** (2004)[4] | DM and renal disease | Reasonable to consider an ACEI for treatment of HTN in most patients with DM. An ACEI (in patients with type 1 or type 2 DM) or an angiotensin II receptor antagonist (in patients with type 2 DM) is considered first-line therapy for the prevention of or slowing the progression of nephropathy. An angiotensin II receptor antagonist should be strongly considered in the treatment of patients with HTN, type 2 DM, macroalbuminuria, and renal insufficiency |
| NKF K/DOQI (2004)[5] | DM and nonDM kidney disease | Patients with diabetic kidney disease, or nondiabetic kidney disease with spot urine total protein/creatinine ratio $\geq$ 200mg/g, with or without HTN, should receive treatment with an ACEI or an angiotensin II receptor antagonist |

* The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure
** Guidelines of the American College of Cardiology/American Heart Association for the Diagnosis and Management of Chronic Heart Failure in the Adult
*** Position statement of the American Diabetes Association
****National Kidney Foundation Kidney Disease Outcome Quality Initiative Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease

The first angiotensin II receptor antagonist to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of HTN was losartan potassium, in 1995. At the present time, seven angiotensin II receptor antagonists are available in the United States: candesartan cilexetil, eprosartan mesylate, irbesartan, losartan potassium, olmesartan medoxomil, telmisartan, and valsartan. All angiotensin II receptor antagonists are approved by the FDA for the treatment of patients with HTN.[6,7-13] Other FDA approved indications are listed in Table 2.

Table 2. FDA Approved Indications for the Angiotensin II Receptor Antagonists

AIIRA	HTN	HTN/LVH*	HF**	Post-MI***	DM Nephropathy****
Candesartan	X		X		
Eprosartan	X				
Irbesartan	X				X
Losartan	X	X			X
Olmesartan	X				
Telmisartan	X				
Valsartan	X		X	X	

* Reduction in the risk of stroke in patients with HTN and LVH (the manufacturer's product information also states that this benefit does not apply to black patients)
** Candesartan: Treatment of HF [New York Heart Association (NYHA) class II-IV] in patients with left ventricular systolic dysfunction (ejection fraction $\leq$ 40%) to reduce CV death and to reduce HF hospitalizations; candesartan has an additive on these outcomes when used with an ACEI. Valsartan: Treatment of HF (NYHA class II-IV). Heart failure hospitalizations were significantly reduced with valsartan. Manufacturer's product information states that there is no evidence that valsartan provides added benefits when it is used with an adequate dose of an ACEI
*** Indicated to reduce CV mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following MI
**** Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (> 300mg/day for irbesartan; urinary albumin to creatinine ratio $\geq$ 300mg/g for losartan) in patients with type 2 DM and HTN

This review evaluates the comparative efficacy and safety of the different angiotensin II receptor antagonists in patients with HTN, recent MI, HF, nephropathy, and those at high cardiovascular risk.

Scope and Key Questions

The purpose of this review is to compare the safety and effectiveness of angiotensin II receptor antagonists for specific indications or patient populations. We developed the scope of the review by writing preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. In consultation with the participating organizations, we selected the following key questions to guide this review:

1. For adult patients with essential hypertension, high cardiovascular risk factors, recent myocardial infarction, heart failure, diabetic or nondiabetic nephropathy, do angiotensin II receptor antagonists differ in efficacy as seen in results from head-to-head trials, active-controlled trials, placebo-controlled trials, or systematic reviews?

    The selected indications/patient populations are further defined with the outcomes of interest listed below:

    a. Essential hypertension ($\geq$ 140/90 mm Hg) with and without compelling indications: history of coronary heart disease (CHD); other cardiovascular disease (CVD), such as cerebrovascular (carotid) disease, peripheral vascular disease, or a history of stroke; other risk factors for coronary artery disease/CVD, such as diabetes, smoking or hyperlipidemia; or renal insufficiency. The outcomes of interest for this indication are:

        i. All-cause and cardiovascular mortality

        ii. Cardiovascular events (stroke, MI, or development of HF)

        iii. End-stage renal disease (including dialysis or need for transplantation) or clinically significant or permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)

        iv. Quality of life

    b. High cardiovascular risk including patients who have a history of CHD/CVD, or a combination of other risk factors for CHD/CVD, such as diabetes, smoking, microalbuminuria, left ventricular hypertrophy (LVH) and hyperlipidemia. These patients may or may not have hypertension as well. The outcomes of interest for this indication are:

        i. All-cause and cardiovascular mortality

        ii. Cardiovascular events (stroke, MI, or development of HF)

        iii. Quality of life

    c. Recent myocardial infarction including patients who have had a recent MI and who have normal left ventricular function or asymptomatic left ventricular dysfunction. The outcomes of interest for this indication are:

        i. All-cause and cardiovascular mortality

        ii. Cardiovascular events (usually, development of HF)

        iii.   Quality of life

d. Heart failure including patients who have symptomatic HF due to left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) < 45%] with or without hypertension or with sustained LVEF > 45%, with or without hypertension. The outcomes of interest for this indication are:

        i.   All-cause and cardiovascular mortality

        ii.   Symptomatic improvement (heart failure class, functional status, visual analogue scores, exercise tolerance)

        iii.   Hospitalizations for HF

        iv.   Quality of life

e. Nephropathy including patients who have laboratory evidence of nephropathy, such as albuminuria or decreased creatinine clearance due to diabetes or non-diabetic causes. The outcomes of interest for this indication are:

        i.   End-stage renal disease (including dialysis or need for transplantation) or clinically significant or permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)

        ii.   Quality of life

2. For adult patients with essential hypertension, high cardiovascular risk factors, recent myocardial infarction, heart failure, diabetic or nondiabetic nephropathy, do angiotensin II receptor antagonists differ in safety or adverse events? The outcomes of interest with regard to safety include:

a. Overall adverse effect reports

b. Withdrawals due to adverse effects

c. Serious adverse events reported (including mortality)

d. Specific adverse effects or withdrawals due to specific adverse events (e.g., renal impairment, cough, and angioedema)

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one angiotensin II receptor antagonist is more effective or associated with fewer adverse events (e.g., renal insufficiency)? Evidence unique to minority and ethnic groups are of particular interest.

METHODS

Literature Search

To identify articles relevant to each key question, we searched Medline (1989 to November 2003), Embase (1991 to 4th Quarter 2003), the Cochrane Central Register of Controlled Trials (3rd Quarter 2003), and reference lists of included review articles. In electronic searches, we combined terms for drug names, indications (*heart failure, hypertension, diabetes, myocardial infarction*), and included study designs (*randomized controlled trials, systematic reviews*), all limited to human and English language (see Appendix A for complete search strategies). Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (ProCite for Windows, Version 5.0.3.).

Study Selection

We included English-language reports of randomized controlled trials that evaluated and included the angiotensin II receptor antagonists (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan) in patients with essential hypertension, high cardiovascular risk factors, recent myocardial infarction, heart failure, or diabetic or nondiabetic nephropathy and reported an included outcome. Included trials evaluated an angiotensin II receptor antagonist compared with another angiotensin II receptor antagonist, an ACEI or antihypertensive agent from another class (e.g., beta-adrenergic blockers, calcium channel blockers), or placebo.

To evaluate efficacy we included only controlled clinical trials. The validity of controlled trials depends on how they are designed. Properly randomized controlled trials are considered the highest level of evidence for assessing efficacy.[14] Clinical trials that are not randomized or blinded, and those that have other methodological flaws, are less reliable, but are also discussed in the report.

Head-to-head trials of one AIIRA against another give direct evidence about comparative efficacy. For many of the treatment outcomes, however, the angiotensin II receptor antagonists were evaluated only against an ACEI. Although these trials provide indirect evidence as to the comparative efficacy of these agents, heterogeneity in study designs, doses used, inclusion criteria, and outcomes assessed make it difficult to determine the comparative efficacy of angiotensin II receptor antagonists from these studies.

Clinical trials as well as observational cohort studies were included to evaluate rates of adverse events. Clinical trials typically exclude patients who have experienced an adverse event on the therapy being evaluated, or include a patient population where the risk of an adverse event is minimized to avoid a high dropout rate. Observational studies are a useful supplement to clinical trials data for adverse events because they may include a broader patient population with a large number of patients evaluated over a long period of time. Many of the clinical trials on the angiotensin II receptor antagonists included large patient populations with a long follow-up period, but not all were large or designed to rigorously evaluate adverse events. Only trials including more than 1,000 patients that were conducted for at least one year were included in the assessment of adverse events, unless the main objective of the trial was to evaluate a specific adverse event.   In order to evaluate the safety of the angiotensin II receptor antagonists, overall

adverse effect reports, withdrawals due to adverse effects (a marker of more serious adverse events), serious adverse events reported (including mortality), and specific adverse effects or withdrawals due to specific adverse events (e.g., renal impairment, cough, and angioedema) were abstracted.

Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results if available and if the trial did not report high overall loss to follow-up.

Data were abstracted by one reviewer and checked by a second reviewer. A quantitative analyst abstracted statistical data.

Quality Assessment

The quality of included studies was assessed by evaluating the internal validity (e.g., randomization and allocation concealment; the similarity of compared groups at baseline; specification of eligibility criteria; blinding of assessors, care providers, and patients; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; use of intention-to-treat analysis; post-randomization exclusions) and external validity (e.g., number screened/eligible/enrolled; use of run-in/washout periods or highly selective criteria; use of standard care in control group; source/role of funding; overall relevance).

Trials that had substantial methodological shortcomings in one or more categories were rated poor quality; trials which met all criteria, were rated good quality; the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are likely to be valid, while others are only probably valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as true differences between the compared drugs.

Appendix B also shows the criteria that were used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. Observational studies were rated as good quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the trial. 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 set of studies relevant to the question.

Extraction of Adverse Event Data

We did not identify any trials that directly compared the relative frequency of adverse events of angiotensin II receptor antagonists. We relied on an indirect method of assessing relative adverse events, by calculating the frequency of adverse events of each drug compared to placebo, and then comparing these frequencies across drugs. Each placebo-controlled trial of

angiotension receptor II medications was examined to determine whether it reported data on adverse events. Adverse events were recorded onto a spreadsheet that identified each medication group, the description of the adverse event as listed in the original article, and the number of subjects in each group. We then abstracted the number of events or percent of people with each adverse event. We assumed that each event represents a unique person.

After abstracting the data, we identified mutually exclusive subgroups of similar events, based on clinical expertise. Our subgroups included: hypotension, dizziness and vertigo, increased serum creatinine, cough, hyperkalemia, bronchitis and other respiratory infections, nausea and vomiting, angioedema, headache, and gastrointestinal disorders.

For each adverse event subgroup, we reported the number of trials that provided data for any event in the subgroup. If a report of a trial mentioned a particular type of adverse event in the discussion but did not report data on that adverse event, we did not include that trial in that particular event's analysis. In other words, we did not assume zero events occurred unless the trial report specifically stated that zero events were observed. We also report the total number of individuals in the medication groups who were observed to have experienced the event and the total number of patients in the medication groups in those trials. We then report the analogous counts for the placebo groups in the relevant trials.

Meta-Analysis of Adverse Event Data

An odds ratio was calculated for those subgroups that just had one trial. For subgroups of events that had at least two trials we performed a meta-analysis to estimate the pooled odds ratio and its associated 95% confidence interval when able. Given that many of the events were rare, we used exact conditional inference to either estimate an odds ratio for a single study or to perform the pooling if meta-analysis was warranted, rather than applying the usual asymptotic methods that assume normality. Asymptotic methods require corrections if zero events are observed, and generally, half an event is added to all cells in the outcome-by-treatment (two-by-two) table in order to allow estimation, because these methods are based on assuming continuity. Such corrections can have a major impact on the results when the outcome event is rare. Exact methods do not require such corrections. We conducted the meta-analysis using the statistical software package StatXact.[15]

Any significant pooled odds ratio greater than one indicates the odds of the adverse event associated with medication is larger than the odds associated with being in the placebo group. For those odds ratios that were pooled, the Zelen's[16] test for homogeneity was performed. A significant value of this test indicates that heterogeneity between the trials has been detected.

Since none of the trials directly compared adverse events between medications, we assessed the comparison of medication versus placebo. If the confidence intervals for different angiotension II receptor antagonists overlapped, then we could not conclude that the odds between medications were significant.

Update 1

For Update 1, we searched Medline, Embase, and the Cochrane Central Register of Controlled Trials (November 2003 to June 2005) following the search methodology described above. We selected new studies, performed data abstraction, and updated our adverse event meta-analysis using methods identical to those used originally.

RESULTS

Overview

Searches identified 1028 total citations: 742 from the Cochrane Library, 144 from MEDLINE, and 84 from EMBASE. Additional review identified 38 citations from reference lists, and 20 from pharmaceutical company submissions. For Key Question #1 (clinical endpoints), we included 43 randomized controlled trials and 3 systematic reviews. Twenty-two clinical trials were excluded for the following reasons: wrong outcome (18); wrong publication type (2); wrong design (2). For Key Question #2 (safety), we included 8 controlled trials and 1 observational study. Eighteen clinical trials were excluded for the following reasons: wrong outcome (11); wrong drug (1); wrong publication type (5); wrong design (1). For Key Question #3 (subgroups), we included 12 controlled trials and excluded 4 clinical trials for the following reasons: wrong outcome (2); wrong population (1); wrong design (1) (Figure 1 (Results of Literature Search). Appendices C and D list the included and excluded articles, respectively.

For the 2005 Update we identified 684 new citations: 290 from Cochrane, 112 from MEDLINE, and 275 from EMBASE. Additional review identified one citation from reference lists, six from pharmaceutical company submissions, and four from our expert's library. Forty-four articles were requested. Eleven were excluded for the following reasons: wrong outcome (7); study duration (2); population not included (1); wrong study design (1). For Key Question #1 (clinical endpoints), we included 21 randomized controlled trials and 1 systematic review. For Key Question #2 (safety), we included no controlled trials and two observational studies. For Key Question #3 (subgroups), we included 6 controlled trials (these are not mutually exclusive).

Most of the randomized trials had good/fair internal validity, and were applicable to community practice. Of those studies that stated a funding source, all were funded by the pharmaceutical industry, and industry employees often were involved in data management or served as co-authors.

Key Question 1.

For adult patients with essential hypertension, high cardiovascular risk factors, recent myocardial infarction, heart failure, diabetic or nondiabetic nephropathy, do angiotensin II receptor antagonists differ in efficacy?

Key Question 1a.

In patients with essential hypertension, what is the comparative efficacy of different angiotensin II receptor antagonists in all-cause and cardiovascular mortality, cardiovascular events (stroke, MI, or development of HF), end-stage renal disease (including dialysis or need for transplantation) or clinically significant or permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance), or quality of life?

Summary

We found no head-to-head trials that address the specified outcomes. Placebo-controlled trials were not useful in assessing comparative efficacy of the angiotensin II receptor antagonists. There were no comparative data with the angiotensin II receptor antagonists and their effects on quality of life. Only one active-controlled trial evaluating morbidity and mortality compared treatment with eprosartan to that of a dihydropyridine calcium channel blocker and reported that eprosartan reduced the combined primary endpoint of all-cause mortality, and CV and cerebrovascular events in patients with HTN and a history of a cerebrovascular event compared to control therapy. Interpretation of the active-controlled trials that evaluated quality of life was limited by the use of different scales and different comparator agents.

Head-to-head trials

We identified no relevant head-to-head trials.

Active-controlled trials

We identified one active-controlled trial of fair quality that evaluated the effect of an angiotensin II receptor antagonist compared to a dihydropyridine calcium channel blocker on all-cause mortality, and CV and cerebrovascular mortality[17] (also see discussion of placebo controlled trial with open-label antihypertensive therapy below).

One active-controlled trial of fair quality evaluated the effect of losartan or enalapril on renal function and quality of life.[18]

We identified six active-controlled trials (two with placebo control), five trials of fair quality that specifically evaluated the quality of life in patients with HTN being treated with losartan,[19, 20] candesartan,[21] or eprosartan,[22, 23] and one trail of poor quality evaluating quality of life in patients with HTN who were switched from a dihydropyridine calcium channel blocker to candesartan.[24]

The active-controlled trials were rated fair quality due to lack of reporting the method for randomization and/or concealment and the method for masking was often not described. In one trial, an open-label design was used, and in two trials, the exclusion criteria were not reported, and only three trials used intent-to-treat analyses. One trial was rated as poor due to the open-label design, lack of randomization, and lack of detailed selection criteria, all of which could lead to bias. Details of these trials are included in Evidence Table 1 and Quality Table 1.

Another active-controlled trial, Losartan Intervention For Endpoint reduction in hypertension study (LIFE),[25] in patients with HTN and LVH (a risk factor for CV complications in patients with HTN), will be discussed in the section on patients with high CV risk factors. Another active-controlled trial identified in the update process, Valsartan Antihypertensive Long-term Use Evaluation (VALUE)[26] in patients with hypertension at high CV risk, will also be discussed in the section on patients with high CV risk factors.

Nine active-controlled trials were excluded due to the wrong outcome[27-34] and wrong publication type.[35]

All-cause mortality, Cardiovascular mortality, and Cardiovascular events

The Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) study, a prospective, randomized, open, blinded endpoint trial, evaluated 1352 patients with a history of HTN and cerebrovascular event, treated with eprosartan or nitrendipine, for the combined primary endpoint of all-cause mortality, cerebrovascular events, and CV events. The combined primary endpoint was significantly reduced with eprosartan compared to nitrendipine, with an incidence density per 100 person years (ID) of 13.25% vs. 16.71%, respectively; and an ID ratio of 0.79 (95% CI 0.66-0.96; P=0.014). The individual components of the primary endpoint were also reduced with eprosartan (fatal and nonfatal CV events: IDR 0.75 95% CI 0.55-1.02; P=0.061 and fatal and nonfatal cerebrovascular events: IDR 0.75 95% CI 0.55-0.97; P=0.026), with the reduction in cerebrovascular events achieving statistical significance. The reduction in BP was similar between the treatment groups with a mean BP at the end of the study or final visit of $137.5\pm16.7/80.8\pm8.9$ mm Hg on eprosartan and $136.0\pm15.6/80.2\pm8.8$ mm Hg in the nitrendipine group.[17]

End-stage renal disease or deterioration of renal function

One, long-term, randomized, double-blind, controlled trial[18] evaluated the effect of losartan on glomerular filtration rate (GFR) compared to enalapril in patients with HTN where there was an increase with both losartan (96.6 ± 32.3ml/min to 108.6 ± 31.12ml/min; P<0.005 vs. baseline) and enalapril (94.8 ± 31.1ml/min to 99.8 ± 19.6ml/min; P=0.085 vs. baseline) after 3 years of therapy. Between-group comparisons were not reported.

Quality of life

The results evaluating quality of life in patients with HTN are summarized in Table 3.

Table 3. Comparison of Quality of Life in Patients with Hypertension

Drug	Analyzed	Duration	QOL tool	QOL results	Cough
Losartan vs. HCTZ[19]	69	2.2 years	46 item questionnaire for patients w/HTN	Losartan (P<0.01) and HCTZ (P<0.02) improved vs. baseline Losartan > HCTZ (P<0.001)	NA
Losartan vs. Losartan plus HCTZ vs. Amlodipine[20]	787	12 weeks	PGWB index	Losartan (P<0.001) and Losartan + HCTZ (P<0.002) improved vs. baseline Amlodipine vs. baseline (NS) Losartan vs. Amlodipine: Positive well-being (P=0.005); General health (P=0.097)	NA
Candesartan vs. Enalapril vs. Placebo*[21]	154	8 weeks	Minor Symptom Evaluation	Minor changes (data NR) No significant difference except contentment Candesartan > Placebo (P=0.03)	Candesartan vs. Placebo (NS) Candesartan < Enalapril (P<0.001)
Eprosartan vs. Enalapril vs. Placebo*[22]	132	6 weeks	PGWB index	No significant differences between treatments in their effects on QOL	Placebo= Eprosartan < Enalapril (NS after adjustment)
Eprosartan vs. Enalapril[23]	523	26 weeks	PGWB index	No significant differences between treatments at monotherapy endpoint (without HCTZ)	Eprosartan < Enalapril (P=0.001) at

				Eprosartan improved self-control (P=0.016) vs. Enalapril; improvement with Enalapril vs. Eprosartan if baseline total score ≤ 119 (P=0.041) at study endpoint	monotherapy endpoint
Losartan vs. Enalapril[36]	42	3 years (QOL at 12 weeks)	Battery-of-scales QOL instrument	No significant differences between treatments for all domains (data not reported) except bother due to cough (see Cough)	Enalapril > bother due to cough (12%) vs. losartan (2%) (P=0.01)

* History ACEI-induced cough

It is difficult to compare the effect of the angiotensin II receptor antagonists studied on quality of life as either different quality of life tools were used or drugs from different classes were used as comparators. Three trials used the validated Psychological General Well-Being (PGWB) index to evaluate quality of life.[20, 22, 23] In the trial with losartan,[20] the total score at baseline was 107.5 which improved after 12 weeks to 110.0 (P<0.001). Patients on losartan had a statistically significant improvement in anxiety, depressed mood, positive well-being, and vitality, which were not significantly improved with amlodipine. The difference in total score between losartan and amlodipine was 1.9 (P=0.058). To put this in context, the authors reported maximum differences in general well-being scores of 3 to 4 points for comparisons in studies of an ACEI and other antihypertensive therapies (e.g., atenolol, methyldopa, propranolol, verapamil). In another trial,[22] the baseline total score for eprosartan was 104 with a decrease to 101.1 (significance not reported) at 6 weeks. In another trial with eprosartan,[23] the baseline total score of 108 improved to 108.4 at study endpoint (that included the addition of open-label HCTZ in both treatment groups; details not shown for this or monotherapy endpoint).

Placebo-controlled trials

Three multicenter, placebo-controlled trials of fair quality were included in the analysis.[37-39] These trials were rated fair due to post-randomization exclusions and the original placebo-controlled design included the addition of open-label antihypertensive therapy,[37] inadequate description of method for randomization and allocation concealment,[38] and post-randomization exclusions or not specifying exclusion criteria[39] Details of these trials are included in Evidence Table 2 and Quality Table 2. In addition, three subgroup analyses of the Study on Cognition and Prognosis in the Elderly (SCOPE) were included in the update.[40-42] Ten placebo-controlled trials were excluded for the following reasons: wrong outcome;[43-49] wrong publication type;[50] wrong design,[48, 49, 51] and wrong population.[52]

The Study on Cognition and Prognosis in the Elderly[37,53] was designed as a placebo-controlled trial, but due to ethical reasons, the protocol specified recommendations for adding open-label antihypertensive therapy. This was a large, multicenter, double-blind, parallel group study with a mean duration of 3.7 years, that randomized 4964 patients to treatment with candesartan 8mg once daily (titrated to 16mg if BP > 160/85 mm Hg) or placebo. Open-label HCTZ or other antihypertensive agents were added according to the protocol. As a result, 84% of patients in the placebo group and 75% in the candesartan group received other antihypertensive therapy).

The Irbesartan Microalbuminuria type 2 Diabetes Mellitus in Hypertensive Patients (IRMA 2) trial[38] randomized 590 patients with HTN and type 2 DM and microalbuminuria to irbesartan 150 mg, irbesartan 300 mg or placebo for a mean follow-up of 2.6 years. The primary endpoint of this trial was time to progression from microalbuminuria to onset of diabetic

nephropathy, with secondary endpoints including change in creatinine clearance (CrCl), level of urinary albumin excretion (UAE), and restoration of normoalbuminuria.

A recent trial enrolled 56 patients with HTN and renal insufficiency, evaluating the effect of 6 months therapy with valsartan 80mg daily or placebo on the change from baseline GFR.[39]

All-cause mortality

All-cause mortality, a secondary endpoint of SCOPE,[53] was not significantly different in the candesartan group compared to active control.

Cardiovascular mortality

In SCOPE,[53] the secondary endpoint of CV mortality was not significantly different in the candesartan vs. active control group.

Cardiovascular events

A first major CV event (CV death, non-fatal MI or non-fatal stroke) was the primary endpoint in SCOPE[53] and occurred in 9.8% patients in the candesartan group and in 10.9% patients in the active control group (P=0.19). Of the pre-specified secondary endpoints, only non-fatal stroke was reduced significantly with candesartan compared to active control (2.8% vs. 3.8%, respectively; risk reduction of 27.8%; 95% CI 1.3-47.2; P=0.04). A reduction in all strokes with candesartan approached statistical significance (risk reduction of 23.6%; P=0.056). Mean BP was reduced to 145.2/79.9 mm Hg in the candesartan group vs. 148.5/81.6 mm Hg in the control group (mean difference in adjusted BP reduction 3.2/1.6 mm Hg favoring candesartan; P<0.001). In a pre-specified subgroup analysis of 1518 patients with isolated systolic hypertension (ISH),[41] only the secondary endpoint of fatal and non-fatal stroke was reduced with candesartan compared to control therapy (2.7% vs. 4.6%, respectively; risk reduction of 42%; P=0.05). When the primary endpoint results were evaluated based on pre-specified subgroups including age, gender, DM, history of stroke, smoking, and CV risk, the only subgroup with a significant difference between candesartan and the control group was in 97 patients with a history of stroke (risk reduction of 64%, P=0.004 vs. 5%, P=0.591 in patients without; P=0.008 for interaction).[40]

End-stage renal disease or deterioration of renal function

Renal function was not a pre-specified endpoint in the SCOPE trial. In IRMA-2,[38] the primary endpoint of time to progression from microalbuminuria to onset of diabetic nephropathy occurred in 5.2% of patients in the irbesartan 300mg treatment group and in 9.7% of patients on irbesartan 150mg compared to 14.9% of patients on placebo. The primary endpoint was reduced in patients on irbesartan 300mg compared to placebo [hazard ratio (HR) 0.30 95% CI 0.14-0.61; P<0.001; NNT=8 95% CI 5-19] but not in patients on irbesartan 150mg. Systolic BP was lower (P=0.004) in the irbesartan groups compared with placebo (average BP: irbesartan 150mg 143/83 mm Hg; irbesartan 300mg 141/83 mm Hg; placebo 144/83 mm Hg) but the benefit seen with irbesartan 300mg was similar regardless of blood pressure. The secondary endpoint of change in CrCl was not significant between groups.

The trial comparing the effect of valsartan and placebo on GFR reported no significant difference in the least squares mean endpoint/baseline ratio between the two treatment groups (P=0.577).[39]

Quality of life

Only the subgroup analysis of SCOPE[42] reported results on quality of life. The Subjective Symptoms Assessment Profile (SSA-P) and the EuroQol Health Utility Index (EuroQol) were used in addition to the PGWB index to evaluate quality of life in 2850 patients enrolled in SCOPE.[23] At baseline, the PGWB total score was similar for patients on candesartan (106.0) compared to the control group (106.3). The difference in change from baseline in total score was not statistically significant between the two groups, although the difference was statistically significant for anxiety (P=0.01) and positive well-being (P=0.04), in favor of treatment with candesartan. The difference in change between the two treatment groups was statistically significant in favor of candesartan for the Cardiac symptom score (heart beating rapidly or slowly, or palpitations) (P=0.03) as part of the SSA-P evaluation, and for Current health (P=0.008) in the EuroQoL assessment.

Systematic reviews

We identified one good quality systematic review[54] that evaluated the effect of the angiotensin II receptor antagonists as antihypertensive therapy in patients with DM. The review and meta-analysis concluded that antihypertensive therapy with an angiotensin II receptor antagonist in patients with DM did not significantly reduce total mortality or CV morbidity and mortality compared to placebo or standard antihypertensive therapy. A statistically significant benefit was seen in reducing ESRD compared to placebo [odds ratio (OR) 0.73 95% CI 0.60-0.89] by combining data from two of the three trials.

Key Question 1b.

In patients with high cardiovascular risk factors, what is the comparative efficacy of different angiotensin II receptor antagonists in all-cause and cardiovascular mortality, cardiovascular events (stroke, MI, or development of HF), or quality of life?

Summary

No head-to-head trials were identified. Two large, long-term, randomized active-controlled trials evaluating cardiac morbidity and mortality were identified. One trial comparing losartan with atenolol in patients with HTN and LVH reported superiority for the outcomes of the primary composite endpoint of CV morbidity and mortality (primarily due to the reduction in stroke) with losartan. Another trial comparing valsartan to amlodipine in patients with HTN at high CV risk reported no difference in the primary composite endpoint of cardiac morbidity and mortality between treatment groups. No conclusions about the comparative efficacy of different angiotensin II receptor antagonists for patients at high CV risk can be drawn.

Head-to-head trials

We identified no relevant head-to-head trials.

Active-controlled trials

We identified two large, active-controlled trials that evaluated cardiac morbidity and mortality in patients at high CV risk. The LIFE study[55] compared the effect of losartan to the beta-adrenergic blocker atenolol in reducing CV morbidity and mortality in patients with HTN and LVH. Four substudies were also conducted in the patients enrolled in the LIFE study that evaluated patients without vascular disease,[56] patients with ISH,[25] patients with DM,[57] and patients by black or non-black ethnic background.[58] The VALUE trial[26] evaluated treatment with valsartan compared to the dihydropyridine calcium channel blocker amlodipine on reducing cardiac morbidity and mortality in patients with HTN at high CV risk. One smaller, open-label trial compared the effect of candesartan to a control group in reducing the composite endpoint of revascularization, nonfatal MI, or CV death in patients with a history of coronary intervention.[59] These trials are described in detail in Evidence Table 3 and Quality Table 3. The results of one active-controlled trial that was excluded in the original report (wrong outcome; reported results of BP reduction with pending cardiac morbidity and mortality results),[60] is now included in the update (VALUE trial).[26]

The LIFE study was a large, multicenter, randomized, double-blind, active-controlled, parallel-group trial conducted in the U.S. and Europe, enrolling 9193 patients with treated or untreated HTN and LVH documented by electrocardiogram (ECG), with a mean follow-up of 4.8 years. Patients were randomized to losartan 50mg or atenolol 50mg, with addition of HCTZ 12.5mg and subsequent titration to 100mg of losartan or atenolol and further increase of HCTZ to 25mg and addition of other antihypertensive therapy (excluding angiotensin II receptor antagonists, beta-adrenergic blockers, or ACEIs) to achieve target BP goal < 140/90 mm Hg. The trial was of good quality.[55] The VALUE trial was a large, multicenter, randomized, double-blind, active-controlled, parallel-group study of good quality, enrolling 15245 patients with treated or untreated HTN and at high risk for cardiac events, with a mean follow-up of 4.2 years. Patients were randomized to valsartan (80mg) or amlodipine (5mg) once daily, with upward titration and addition of HCTZ, then other antihypertensive agents (excluding angiotensin II receptor antagonists; ACEIs or calcium channel blockers if not being used for another indication) in a pre-specified protocol to achieve target BP < 140/90 mm Hg.[20, 26]

The randomized trial evaluating treatment with candesartan 4mg daily compared to a control group in 406 patients with a history of coronary intervention was rated poor quality due to the open-label design, lack of placebo control, and unequal use of other medications.[59]

All-cause mortality

All-cause mortality was a pre-specified outcome but not the primary endpoint of the LIFE study and the three substudies. In the overall LIFE study,[55] all-cause mortality occurred in 8% of patients randomized to losartan and was not statistically significantly different compared to a mortality of 9% of patients in the atenolol group (adjusted HR 0.90 95% CI 0.88-1.03; P=0.128). The difference in all-cause mortality also did not achieve statistical significance in the post-hoc subgroup analysis of patients without clinically evident vascular disease.[56] Losartan statistically significantly reduced all-cause mortality compared to atenolol in both the pre-specified substudies with ISH[25] and patients with DM.[57]

In the VALUE trial, there was not a statistically significant difference in all-cause mortality (a pre-specified endpoint) in patients treated with valsartan compared to amlodipine (11% vs. 10.8%, respectively; HR 1.04 95% CI 0.94-1.14; P=0.45).[26]

Cardiovascular mortality

In the LIFE study,[55] the primary endpoint of CV morbidity and mortality (composite CV death, MI, and stroke) occurred in 11% of patients on losartan compared to 13% of patients on atenolol (adjusted HR 0.87 95% CI 0.77-0.98; P=0.021), with a calculated NNT of 56 (95% CI 32-217) for 4.8 years. When CV mortality was analyzed separately, the difference was not statistically significant (P=0.206). The addition of HCTZ and/or other antihypertensive agents were required in similar proportions of patients on losartan and atenolol. The mean BP in the two intervention groups was similar.

The primary composite endpoint of CV morbidity and mortality was decreased in the patients receiving losartan in the subgroup of patients without vascular disease (P=0.008),[56] patients with ISH (P=0.06),[25] and patients with DM (P=0.031).[57]

Cardiac mortality was reported to be similar (i.e., 4% each) in the valsartan and the amlodipine treatment groups when the components of the primary endpoint of VALUE were evaluated separately.[26]

Cardiovascular events

The difference in the primary endpoint of composite CV death, MI, and stroke (as discussed above) with losartan compared to atenolol appeared to be largely due to the difference in stroke. In the losartan group, 5% of patients experienced the endpoint of stroke compared to 7% of patients in the atenolol group (adjusted HR 0.75 95% CI 0.63-0.89; P=0.001).[25] Other CV endpoints including MI, angina or HF hospitalization, coronary or peripheral revascularization, or resuscitated cardiac arrest were not significantly different between patients in the two treatment groups.[25]

As part of the LIFE trial, a subgroup analysis suggested a potential interaction between treatment and the comparison of five categories of different ethnic backgrounds (P=0.057). When further analyzed by comparing post hoc black and non-black treatment groups, the

interaction was statistically significant (P=0.005).[58] In the LIFE trial, there were 533 black patients included (6% of the patient population). In a subgroup analysis of these patients,[58] the primary endpoint (CV death, nonfatal stroke, nonfatal MI) occurred in 46 of 270 patients (17%) on losartan compared to 29 of 263 patients (11%) on atenolol. When the components of the primary endpoint were evaluated separately, stroke occurred in 8.9% of black patients in the losartan group compared to 4.6% of black patients on atenolol (adjusted HR 2.179 95% CI 1.079-4.401; P=0.03). Losartan is approved by the FDA for reducing the risk of stroke in patients with HTN and LVH, although the indication states that there is evidence that this benefit does not apply to black patients.[10]

In the substudies of patients without vascular disease[56] and those with ISH,[25] CV endpoints were not significantly different between patients treated with losartan and atenolol. The incidence of stroke was reduced with losartan in patients without vascular disease (P<0.0001)[56] and in patients with ISH (P=0.02).

Patients in the DM substudy[57] experienced a reduction in HF hospitalizations with losartan compared to treatment with atenolol (P=0.019). All other CV endpoints including stroke, MI, hospitalization for angina, coronary or peripheral revascularization, or resuscitated cardiac arrest were not significantly different between treatment groups.

There was not a statistically significant difference in the primary composite endpoint of cardiac morbidity and mortality (first time to event) between the valsartan and amlodipine treatment groups. Neither were the secondary endpoints of fatal and nonfatal HF or fatal and nonfatal stroke. There was a statistically significant difference in the secondary endpoint of fatal and nonfatal MI which was reported in 4.8% of patients on valsartan compared to 4.1% of patients on amlodipine (HR 1.19 95% CI 1.02-1.38; P=0.02).[26] A difference in BP reduction between the two treatment groups in favor of amlodipine at 1 month (4.0/2.1 mm Hg) and at the end of the study or final visit (reduction from baseline 15.2/8.2 mm Hg with valsartan vs. 17.3/9.9 mm Hg with amlodipine; P<0.0001) was noted. In a subanalysis of 5006 treatment cohort pairs matched by SBP at 6 months, age, sex, presence or absence of previous coronary disease, stroke, or DM, the difference in MI (not specified as fatal or nonfatal) was not statistically significant.[61]

Quality of life

Quality of life was not assessed in any of the active-controlled trials evaluating patients with high CV risk.

Placebo-controlled trials

We identified no relevant placebo-controlled trials.

Systematic reviews

We identified no relevant systematic reviews.

Key Question 1c.

In patients with recent myocardial infarction, what is the comparative efficacy of different angiotensin II receptor antagonists in all-cause and

cardiovascular mortality, cardiovascular events (usually, development of HF), or quality of life?

Summary

In one multicenter, randomized, active-controlled trial, valsartan was shown to be as effective as captopril in reducing all-cause mortality, CV mortality, and CV events in patients with recent MI and at high risk for coronary events.[62] Another multicenter, randomized, active controlled trial with losartan, was unable to show that treatment with losartan was as effective or superior to captopril in reducing all-cause mortality in patients with recent MI and signs or symptoms of HF.[63] As the outcomes of VALIANT and OPTIMAAL differed, whether the results seen with the angiotensin II receptor antagonists are a class effect remains uncertain. It has been suggested that the difference may have been related to the dose selected, but this remains to be proven. There is insufficient evidence from active-controlled trials to determine whether valsartan or losartan are equivalent or superior to one another for this indication.

As there were no head-to-head trials, and long-term outcome data were available with only two of the angiotensin II receptor antagonists, with the two trials being of different design, conclusions regarding comparative efficacy in patients with recent MI cannot be made.

Head-to-head trials

We identified no relevant head-to-head trials.

Active-controlled trials

Two active-controlled trials were identified that evaluated treatment with an angiotensin II receptor antagonist compared to an ACEI in patients with a recent MI and were included in the review (refer to Evidence Table 4 and Quality Table 4).[62, 63] The Valsartan in Acute Myocardial Infarction Trial (VALIANT)[62] enrolled 14,808 patients (from North America, South America, Europe, Africa, and Australia) and compared treatment with valsartan vs. captopril vs. the combination of the two agents with a mean follow-up of 2.1 years. The dose of valsartan was 160mg twice daily and captopril 50mg three times daily. The dose of valsartan used in the group receiving combination therapy was half that of monotherapy. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL)[63] enrolled 5,477 patients (from Europe) and compared losartan at a dose of 50mg once daily to captopril 50mg three times daily with a mean follow-up of 2.7 years. Both were large, multicenter, randomized, controlled trials of good quality that enrolled patients with a recent MI and signs of HF[62-65] or evidence of left ventricular systolic dysfunction based on ejection fraction.[62] Baseline characteristics and use of beta-blockers and aspirin were similar.

All-cause mortality

All-cause mortality was the primary endpoint in both trials, the results of which are presented in Table 4.

In VALIANT,[62] the test for non-inferiority was statistically significant therefore, valsartan was considered to be as effective as captopril in reducing all-cause mortality in this patient population

In OPTIMAAL,[63] all-cause mortality was higher, with a trend toward statistical significance, with losartan compared to treatment with captopril (see Table 4). This trial was unable to confirm its primary hypothesis that losartan was superior or non-inferior compared to treatment with captopril in reducing all-cause mortality. It is unclear whether an optimal dose of losartan (mean 45±12mg per day) was used in the trial. This is being addressed in an ongoing morbidity and mortality trial to evaluate losartan 50mg with losartan 150mg daily in patients with HF.

Both trials performed subgroup analyses that did not find a significant interaction for all-cause mortality stratified by baseline treatment with a beta-adrenergic blocker.[62, 63]

Cardiovascular mortality

Cardiovascular mortality, a secondary endpoint in VALIANT[62] and a pre-specified endpoint in OPTIMAAL,[63] are presented in Table 4.

Table 4. Comparison of VALIANT and OPTIMAAL Trial Results

Outcomes (VALIANT)	Valsartan (N=4909)	Captopril (N=4909)	Valsartan + Captopril (N=4885)	Hazard Ratio (vs. captopril) (97.5% CI)	P value
All-cause mortality*	979 (19.9%)	958 (19.5%)	941 (19.3%)	1.00 (0.90-1.11) 0.98 (0.89-1.09) (combination)	0.98 0.73
CV mortality**	827 (16.8%)	827 (16.9%)	830 (16.9%)	0.98 (0.87-1.09) 1.00 (0.89-1.11) (combination)	0.62 0.95

Outcomes (OPTIMAAL)	Losartan (N=2744)	Captopril (N=2733)	Relative Risk (95% CI)	P value
All-cause mortality*	499 (18.2%)	447 (16.4%)	1.13 (0.99-1.28)	0.069
CV mortality***	420 (15.3%)	363 (13.3%)	1.17 (1.01-1.34)	0.032

* Primary endpoint
** Secondary endpoint
***Pre-specified endpoint

Cardiovascular events

Valsartan was also shown to be non-inferior to captopril for the following secondary CV endpoints: death from CV causes or MI (P<0.001); death from CV causes or HF (P<0.001); death from CV causes, MI, or HF (P<0.001); death from CV causes, MI, HF, resuscitation after cardiac arrest, or stroke (P<0.001). Treatment with the combination of valsartan and captopril did not offer additional benefit compared to captopril alone.[62]

The difference in secondary endpoints of sudden cardiac death or resuscitated cardiac arrest (P=0.072) and fatal or nonfatal MI (P=0.722) were not statistically significant between the losartan and captopril treatment groups.[63] There was also no statistically significant differences

for MI or total mortality; fatal or nonfatal stroke; coronary artery bypass graft (CABG); percutaneous transluminal coronary angioplasty (PTCA); revascularization; first all-cause admission; first admission for HF; CV admission; or non-CV admission.

Quality of life

Results of the quality of life assessments in VALIANT[62] and OPTIMAAL[63] were not reported in the results of these two publications.

Placebo-controlled trials

We identified no relevant placebo-controlled trials.

Systematic reviews

A meta-analysis evaluating the effect of treatment with an angiotensin II receptor antagonist on all-cause mortality and HF hospitalizations included 22 trials of patients with HF (findings reported in Key Question 1d) and 2 trials of patients with high-risk acute MI (VALIANT[62] and OPTIMAAL[63]).[66] Due to heterogeneity of the trials, the results could not be pooled for evaluation of patients with acute MI.

Key Question 1d.

In patients with heart failure, what is the comparative efficacy of different angiotensin II receptor antagonists in all-cause and cardiovascular mortality, symptomatic improvement (HF class, functional status, visual analogue scores, exercise tolerance), hospitalizations for HF, or quality of life?

Summary

There were no head-to-head trials to compare all-cause mortality, CV endpoints, HF hospitalizations, symptomatic improvement, or quality of life among the angiotensin II receptor antagonists in patients with HF. In two placebo-controlled trials of good quality, treatment with candesartan reduced the endpoint of CV death and HF hospitalizations in patients with symptomatic HF where it was either added to standard therapy[67] or to patients not taking an ACEI due to intolerance,[68] but not in patients with a LVEF > 40%.[69] All-cause mortality was not significantly reduced in pooled analysis of these three trials. In a pre-specified analysis of the two trials of patients with LVEF $\leq$ 40%, there was a significant reduction in all-cause mortality.[70] In one good quality placebo-controlled trial,[71] valsartan reduced the combined endpoint of morbidity and mortality in patients with HF who were receiving standard therapy for HF, but did not reduce all-cause mortality. In one active-controlled trial of good quality,[62] losartan did not reduce mortality or CV endpoints compared with an ACEI in patients with HF.

There is good evidence that candesartan and valsartan are beneficial in patients with HF who are unable to tolerate therapy with an ACEI.[68, 72] The evidence is not as clear for patients with HF who are receiving an ACEI and beta-adrenergic blocker, as adding an angiotensin II receptor antagonist resulted in an increase in mortality in one trial with valsartan.[71] Another trial

with candesartan showed a reduction in CV death or HF hospitalization in patients on candesartan, an ACEI, and a beta-adrenergic blocker compared to patients not receiving an angiotensin II receptor antagonist. There was no effect on all-cause mortality.[67] It is difficult to compare the results of these trials as the endpoints varied and there were slight differences in patient populations studied.

      According to results of a meta-analysis including patients with HF, treatment with an angiotensin II receptor antagonist reduced all-cause mortality and HF hospitalizations compared to placebo. Results were not statistically significant compared to treatment with an ACEI.[66]

      Five placebo-controlled trials and eight active-controlled trials, all of fair quality, evaluated symptom improvement or progression of HF in patients with HF. Symptoms of HF were improved with candesartan[73] and losartan,[74, 75] compared to placebo; irbesartan improved exercise capacity although this did not represent a statistically significant difference compared to placebo.[76] Candesartan slowed the progression of HF compared to placebo.[77] Symptoms were similar with candesartan,[78] losartan,[79-81] telmisartan,[82] and valsartan[83] compared to an ACEI, although different ACEI comparators were used. The addition of valsartan to treatment with an ACEI improved symptoms compared to control.[84] Candesartan also improved symptoms in patients with diastolic dysfunction that was not seen with a calcium channel blocker.[85] Three placebo-controlled trials and four active-controlled trials of fair quality evaluated quality of life parameters using the validated MLHF questionnaire in patients with HF. Quality of life was reported to improve with losartan[75] and valsartan[72] compared to placebo and were also similar to treatment with an ACEI.[83, 86] Quality of life was reported to be improved[85] or unchanged with candesartan.[87] Not enough data were available to assess the results with telmisartan compared to an ACEI.[82] No data were available for eprosartan or olmesartan. Due to the use of a modified MLHF instrument in two trials,[75, 85] and differences in reporting results, it is difficult to compare the effect of the angiotensin II receptor antagonists on quality of life in the trials in patients with HF.

      As there were no head-to-head trials, and long-term outcome data were available with only a few of the angiotensin II receptor antagonists, conclusions regarding the comparative efficacy in patients with HF cannot be made.

Head-to-head trials

      We identified no relevant head-to-head trials.

Active-controlled trials

      Eleven active-controlled trials that evaluated the effect of candesartan, losartan, telmisartan, or valsartan in patients with HF were included. One trial was of good quality[88] and ten trials were fair quality (due to inadequate description of randomization and/or allocation concealment, three trials did not report patients who were lost to follow-up, three trials did not use an intent-to-treat analysis, complete data were not available in one trial, and one trial was a pilot study).[89,78-86] Details of these trials are included in Evidence Table 5 and Quality Table 5.

All-cause mortality, cardiovascular mortality, hospitalizations for heart failure

      Treatment with losartan was compared to captopril in 722 patients with NYHA class II to IV HF (31% LVEF) in the ELITE pilot trial (Evaluation of Losartan in the Elderly).[89] Patients

were randomized to losartan (up to 50mg once daily) or captopril (up to 50mg three times daily) for 48 weeks. Patients received standard therapy for HF (74% diuretics; 55% digoxin). Only 16% were on beta-adrenergic blockers at baseline since recruitment began in 1994 and the beneficial effects of beta-adrenergic blockers were not established at that time. The primary endpoint in the ELITE trials was the effect of treatment on serum creatinine (sCr). There was no difference between treatment groups in the rise in sCr during treatment. The secondary endpoints of death and/or HF hospitalization occurred in 9.4% of patients on losartan and 13.2% on captopril (P=0.075). The difference was primarily due to a 46% decrease in all-cause mortality in patients on losartan compared to patients on captopril (4.8% with losartan vs. 8.7% with captopril; P=0.035), which was driven by a reduction in sudden cardiac death. The two treatment groups did not differ in the frequency of HF hospitalizations. Both groups exhibited a significant improvement in NYHA functional class compared to baseline. The unexpected mortality benefit was the basis for development of ELITE II.

In ELITE II,[88] 3,152 patients with NYHA class II-IV HF (31% LVEF) were stratified by beta-adrenergic blocker use (22%) and randomized to losartan 50mg once daily or captopril 50mg three times daily. The primary endpoint was all-cause mortality, with CV events as a secondary endpoint (e.g., sudden cardiac death or resuscitated cardiac arrest). There was no significant difference in all-cause mortality between the treatment groups (17.7% on losartan vs. 15.9% on captopril, HR 1.13; 95% CI 0.95-1.35; P=0.16); although the trial was not designed to determine equivalence, but superiority, of losartan compared to an ACEI. There was no difference between the groups in sudden death or resuscitated cardiac arrest, or HF hospitalizations. It has been hypothesized that the dose of losartan was inadequate to achieve superiority over captopril.[90] A study comparing losartan 50mg with 150mg is currently ongoing to evaluate whether higher doses than used in ELITE II might improve clinical outcomes.

The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study[78, 91] compared candesartan(4mg, 8mg, or 16mg), enalapril (20mg), and the combination of candesartan (4mg or 8mg) with enalapril (20mg) in 768 patients with NYHA class II to IV HF (15% receiving beta-adrenergic blockers). The trial lasted 43 weeks with termination 6 weeks early due to concern by the External Safety and Efficacy Monitoring Committee of an increase in HF hospitalizations with candesartan and candesartan plus enalapril compared to enalapril alone (3 way group comparison P=0.048) and mortality plus HF hospitalization (3 way comparison P=0.058). There was no significant difference in the primary endpoint of exercise tolerance (six-minute walk test), or NYHA functional class between treatment groups.

Symptomatic improvement

Eight studies of fair quality (primarily due to lack of reporting the method for randomization and/or concealment, method for masking was often not described, and only four studies used an intent-to-treat analyses) assessed symptomatic improvement. Three studies evaluated losartan, [79-81,88] one study telmisartan,[82] and two studies valsartan.[83, 84] One study evaluated candesartan in patients with diastolic dysfunction.[85] A pilot study evaluating candesartan is reported above.[78] When these angiotensin II receptor antagonists were compared to captopril or enalapril, there were no clear differences in symptomatic improvement as measured by a variety of methods (e.g., pedometer and corridor walk test, 6-minute walk test, exercise treadmill test, dyspnea-fatigue index, signs and symptoms of HF, improvement in NYHA functional class, bicycle exercise duration). The trial evaluating addition of valsartan to

active controls (i.e., including treatment with an ACEI and loop diuretic, without a beta-adrenergic blocker) reported a statistically significant improvement in NYHA functional class compared to baseline, and compared to control therapy.[84] Candesartan was compared to verapamil in patients with diastolic dysfunction, where exercise duration was significantly improved with candesartan but not with verapamil (between group comparisons not reported).[85] There was no pattern to suggest that one angiotensin II receptor antagonist was superior to any of the others for symptomatic improvement from these studies.

Quality of life

Quality of life was assessed in three studies of fair quality (one had incomplete quality of life data and did not use an intent-to treat analysis, one had unexplained post randomization exclusions, and another did not adequately describe randomization and did not use an intent-to-treat analysis) that compared an angiotensin II receptor antagonist with an ACEI.[82, 83, 86] One study compared losartan with captopril,[86] another valsartan with enalapril,[83] and the other telmisartan with enalapril.[82] One study of fair quality (not an intent-to-treat analysis) reported an improvement in QOL with candesartan but not verapamil in patients with diastolic dysfunction.[85] All four studies evaluated quality of life using the validated Minnesota Living with Heart Failure (MLHF) questionnaire. In general, there were no significant differences in quality of life between the angiotensin II receptor antagonist and the ACEIs studied. There was a statistically significant improvement in communication favoring captopril over losartan, although the clinical significance of this result is unknown.[86]

Placebo-controlled trials

Fifteen placebo-controlled trials were included that evaluated the effect of candesartan, irbesartan, losartan, or valsartan in patients with HF and are described in Evidence Table 6 and Quality Table 6. In addition, one subgroup analysis in elderly patients[92] and one subanalysis of hospitalizations,[93] both with data from a large clinical trial with valsartan,[71] were included in the update, as well as one pooled analysis in patients with low LVEF on candesartan.[94] Seven trials were of good quality,[67-71, 94, 95] eight trials were fair quality (inadequate description of randomization and/or concealment, four studies did not use an intent-to-treat analysis, significant difference in baseline groups in one study, large number of post-randomization exclusions in another)[72, 76,67, 68, 70, 71,73-75, 77, 87, 96] and one was rated as poor quality (due to doses of open-label ACEIs inconsistent, some patients received prohibited medications, and the study did not use an intent-to-treat analysis).[97] Two trials were excluded due to wrong outcome (LVEF and central hemodynamic and neurohormonal effects)[98] and wrong design (dose-finding study).[99] One trial was excluded from the update due to wrong outcome and design.[100]

All-cause mortality, cardiovascular mortality, and hospitalizations for heart failure

The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Overall program[70] incorporated results of three separate randomized, multicenter, double-blind trials evaluating the effect of candesartan 4mg once daily (mean dose 24mg), titrated to 32mg once daily in addition to standard heart failure therapy (diuretics: 83%; ACEI: 0-100% depending on the protocol; beta-adrenergic blockers: 55%; digoxin: 43%; spironolactone:

17%) in 7599 patients with symptomatic heart failure. The primary outcome for the individual CHARM trials was combined CV mortality or HF hospitalizations.[67-69]

The primary outcome for CHARM-Overall[70] was all-cause mortality, which was reduced with candesartan treatment, although of borderline significance (unadjusted HR 0.91 95% CI 0.83-1.00; P=0.055). The secondary endpoint of combined CV death or HF hospitalization was significantly reduced compared to placebo (unadjusted HR 0.84 95% CI 0.77-0.91; P<0.0001).[70]

In a pooled analysis of patients with LVEF $\leq$ 40% (combined data from CHARM-Alternative and CHARM-Added trials), there was a significant reduction in all-cause mortality (HR 0.88 95% CI 0.79-0.98; P=0.018).[70,94] The combined primary endpoint of CV mortality or HF hospitalization occurred in 35.7% of patients on candesartan and 41.3% on placebo (HR 0.82 95% CI 0.74-0.90; P<0.001).[94]

The CHARM-Alternative trial[68] randomized 2028 patients with LVEF $\leq$ 40% with a history of ACEI intolerance to candesartan or placebo, in addition to standard therapy for HF. Cough was the most common reason for ACEI intolerance, reported in 70% of patients. The combined primary endpoint of CV mortality or HF hospitalization occurred in 33% of patients on candesartan and 40% on placebo (unadjusted HR 0.77 95% CI 0.67-0.89; P=0.0004), with a calculated NNT of 14 (95% CI 9-35) patients over 2.8 years. Hospitalizations for HF were reduced by 32%.

The CHARM-Preserved trial[69] enrolled 3023 patients with HF and LVEF > 40%. The primary endpoint of CV mortality or HF hospitalizations did not reach statistical significance (P=0.118).

The CHARM-Added trial[67] randomized 2548 patients with LVEF $\leq$ 40% to candesartan or placebo in addition to standard therapy for HF (ACEIs: 100%; beta-adrenergic blockers: 55%). The combined primary endpoint of CV mortality or HF hospitalization was statistically significantly reduced compared to placebo (unadjusted HR 0.85 95% CI 0.75-0.96; P=0.011), with a calculated NNT of 23 (95% CI 12-156). Hospitalizations for HF and CV mortality were also significantly reduced. Results are presented in Table 5. A significant risk reduction was also seen in the subgroup of patients who received candesartan in combination with an ACEI and beta-adrenergic blocker, which is in contrast to the results of Val-HeFT in this subgroup of patients (discussed in further detail below).

The Valsartan Heart Failure Treatment (Val-HeFT) study[71] included 5,010 patients with NYHA class II-IV HF on standard therapy (diuretics: 85%; ACEI: 93%; beta-adrenergic blockers: 35%; and digoxin 67%). Patients were randomized to therapy with either valsartan (40mg twice daily, titrated to a target of 160mg twice daily with a mean of 254mg per day) or placebo. The two primary endpoints were all-cause mortality and the combined endpoint of mortality and morbidity (i.e., cardiac arrest with resuscitation, HF hospitalization, or intravenous inotropic agents or vasodilators for over 4 hours). Results are summarized in Table 5. Overall mortality was similar in patients on valsartan compared to patients on placebo. The combined primary endpoint was statistically significantly reduced in patients on valsartan compared to placebo with a calculated NNT of 31 patients (95% CI 17-140) over 1.9 years. This, however, has been reported to be largely due to the patients not receiving an ACEI (7%).[13] There was also a statistically significant reduction in HF hospitalizations with valsartan compared to placebo. All-cause mortality (as first event) was higher in patients on valsartan compared to patients receiving placebo (14.2% vs. 12.6%, respectively). According to a subgroup analysis, there was a statistically significant increase in the risk of mortality (P=0.009) and a non-significant trend toward an increased risk of combined morbidity and mortality (P=0.10) in patients receiving

valsartan in addition to an ACEI and beta-adrenergic blocker. Patients who were not on an ACEI or beta-adrenergic blocker experienced a statistically significant reduction in mortality (P=0.012). In the subgroup of 366 patients not on an ACEI, there was a statistically significant lower risk of all-cause mortality [relative risk (RR) 0.67, 95% CI 0.42-1.06; P=0.017] and a statistically significant lower risk of the combined morbidity and mortality endpoint (RR 0.56, 95% CI 0.39-0.81; P<0.0001) on valsartan.[71,72] A subgroup analysis of elderly vs. non-elderly patients reported a statistically significant effect of valsartan on reducing HF hospitalizations in both patient subgroups. The effect on all-cause mortality, combined morbidity and mortality, or CV death was not statistically significant when analyzed by age group.[92]

In patients on an ACEI alone (i.e., without a beta-adrenergic blocker), there was a significant reduction in the combined endpoint (P=0.002) and a non-significant reduction in mortality with valsartan compared to placebo. A summary of results of CHARM-Added and Val-HeFT are included in Table 5.

Table 5. Comparison of CHARM-Added and Val-HeFT Trial Results

Outcomes (CHARM-Added)	Candesartan (N=1276)	Placebo (N=1272)	Unadjusted Hazard Ratio (95% CI)	P value	ARR**	NNT** (3.4 years)
All-cause mortality	377 (30.0%)	412 (32.0%)	0.89 (0.77-1.02)	0.086	NA	NA
CV mortality or HF hospitalization*	483 (37.9%)	538 (42.3%)	0.85 (0.75-0.96)	0.011	4.4%	23
CV mortality	302 (23.7%)	347 (27.3%)	0.84 (0.72-0.98)	0.029	3.6%	28
HF hospitalization	309 (24.2%)	356 (28.0%)	0.83 (0.71-0.96)	0.014	3.8%	27

Outcomes (Val-HeFT)	Valsartan (N=2511)	Placebo (N=2499)	Relative Risk (97.5% CI)	P value	ARR**	NNT** (1.9 years)
All-cause mortality*	495 (19.7%)	484 (19.4%)	1.02 (0.88-1.18)***	0.80	NA	NA
All-cause mortality (1st event) and morbidity*	723 (28.8%)	801(32.1%)	0.87 (0.77-0.97)	0.009	3.3%	31
HF hospitalization	348 (13.8%)	454 (18.2%)	0.725	<0.001	4.4%	23

* Primary endpoint
** Calculated value
*** 98% Confidence Interval

In both the Val-HeFT[71] and CHARM-Added[67] trials, the subgroup of patients receiving an angiotensin II receptor antagonist in combination with an ACEI and beta-adrenergic blocker was analyzed. Results of the subanalysis of Val-HeFT[71] showed a significant increase in all-cause mortality when valsartan was used in combination with an ACEI and beta-adrenergic blocker, but a significant reduction in mortality and combined morbidity and mortality in patients on valsartan who were not receiving concomitant treatment with an ACEI. The FDA labeling for valsartan states that it is indicated for the treatment of HF (NYHA class II-IV) and that HF hospitalizations were significantly reduced with valsartan. Labeling also includes a statement that there is no evidence that valsartan provides additional benefit in patients receiving adequate doses of an ACEI,[13] as the trend for benefit in patients receiving an ACEI with valsartan vs.

placebo was largely due to patients who received less than the recommended dose of an ACEI.[13] The CHARM-Added trial[67] evaluated addition of candesartan to patients on an ACEI, with slightly over half on concomitant therapy with a beta-adrenergic blocker. Results showed a significant reduction in the combined primary outcome of CV death or HF hospitalizations. The difference in all-cause mortality (not a pre-specified endpoint) was not statistically significant. The primary endpoint was reduced in patients on a beta-adrenergic blocker (pre-specified subgroup) in addition to an ACEI and candesartan. All-cause mortality was not significantly different in patients treated with candesartan and a beta-adrenergic blocker and ACEI compared to patients in the placebo group. Candesartan is FDA approved for the treatment of HF (NYHA class II-IV) with LVEF $\leq$ 40% to reduce CV death and HF hospitalizations. Labeling also includes a statement that candesartan has an added effect when used with an ACEI for these treatment outcomes.[6]

In a subanalysis of Val-HeFT evaluating the effect of valsartan on hospitalization, there was not a statistically significant difference between treatment and placebo on all-cause hospitalization (as evaluated by the investigator). There was a 22.4% difference in HF hospitalizations in patients treated with valsartan compared to placebo (P=0.002). A statistically significant reduction in HF hospitalization was also seen in the following concomitant treatment subgroups: with an ACEI, without an ACEI, without a beta-adrenergic blocker; with an ACEI but without a beta-adrenergic blocker; neither an ACEI nor beta-adrenergic blocker.[93]

Treatment with valsartan in combination with an ACEI in patients who are unable to take a beta-adrenergic blocker may also be useful as a significant reduction in the combined primary endpoint of morbidity and mortality was seen in this patient subgroup.[71]

In the CHARM-Alternative trial[68] that enrolled patients unable to tolerate an ACEI, treatment with candesartan (with 55% of patients on beta-adrenergic blockers at baseline) reduced the primary outcome of combined CV death or HF hospitalizations. The difference in all-cause mortality (not a pre-specified endpoint) was not statistically significant. It was reported that the benefit was consistent across prespecified subgroups (data not provided in original publication). In a subgroup analysis of patients in Val-HeFT who were not receiving an ACEI,[72] the primary endpoints of all-cause mortality occurred in 17.3% of patients on valsartan compared to 27.1% of patients on placebo (RR 0.67 95% CI 0.42-1.06; P=0.017). The primary endpoint of combined morbidity and mortality occurred in 24.9% of patients on valsartan compared to 42.5% of patients on placebo (RR 0.56 95% CI 0.39-0.81; P<0.001). There was a significant reduction in HF hospitalization (P<0.001) and a reduction in CV mortality that was not statistically significant.

A smaller trial with candesartan evaluated patients previously treated with an ACEI (ACEI discontinued for the study) to determine the effect of candesartan on progression of HF (defined as HF hospitalizations or addition/increase in HF related medication). The trial was terminated early due to a statistically significant benefit seen with candesartan compared to placebo (7.4% vs. 22.2%; ARR 14.8% 95% CI 6.8-22.8%; P=0.0004). The occurrence of CV events were reduced with candesartan compared to placebo (10.8% vs. 22.9%; ARR 12.1% 95% CI 3.6%-20.6%; P<0.01).[77]

Symptomatic improvement

Five trials were designed to evaluate symptomatic improvement,[73-75, 95] in addition to Val-HeFT discussed above.[71] Dose-related improvements in total exercise time (by bicycle ergometry) and the dyspnea-fatigue index was seen with candesartan. In one trial, improvements

in NYHA functional class were seen more frequently with candesartan compared to placebo, although the differences were not statistically significant.[73] In the CHARM program trials, more patients receiving candesartan improved, and not as many patients worsened, in NYHA class compared to placebo.[95] In a study with losartan,[74] at 6 months, NYHA functional class improved from baseline compared to no difference with placebo (P<0.001 losartan vs. placebo). In a cross-over study with losartan,[75] patients treated with losartan experienced a significant increase in exercise time (assessed by treadmill test) compared to baseline and compared to placebo (P<0.05 for both) at 2 weeks. Treatment with valsartan resulted in significant improvements in NYHA class with fewer patients who experienced worsening (P<0.001). There was also a significant improvement in LVEF (P=0.001) and signs and symptoms of HF (P<0.01) with valsartan compared with placebo.[71] Treatment with irbesartan in addition to standard therapy for HF (100% ACEI; 88% beta-adrenergic blocker) reported improvement in submaximal exercise duration compared to baseline (P=0.018) that was not seen with placebo.[76, 95]

Quality of life

The subgroup analysis of patients in Val-HeFT who were not receiving an ACEI,[72] also reported an improvement in quality of life with valsartan (assessed by the validated MLHF questionnaire) that was seen throughout the study but only reported a statistically significant difference at one year. A statistically significant benefit with valsartan was also reported in elderly and non-elderly patients in a subgroup analysis of Val-HeFT.[92] Another trial reported an improvement in quality of life (also assessed by the MLHF questionnaire, modified to assess symptoms over the previous two weeks) with losartan,[75] that was statistically significant compared to placebo (P<0.05). In the 12 week pilot Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE)[87] of 270 patients, quality of life was unchanged with candesartan (as assessed by the MLHF questionnaire), but declined 9.5% with placebo. When patient's perception of treatment on symptoms was evaluated using the McMaster Overall Treatment Evaluation questionnaire in the CHARM trials conducted in North America, more patients receiving treatment with candesartan improved, and less worsened, compared to placebo.[96]

Systematic reviews

The systematic reviews and meta-analyses in patients with HF did not compare treatment of the angiotensin II receptor antagonists to each other. One meta-analysis of good quality in patients with HF,[101] found that an angiotensin II receptor antagonist was not superior to treatment with an ACEI in reducing all-cause mortality although there was a trend in decreasing mortality and hospitalization compared to placebo in patients who were not treated with an ACEI. This systematic review included 17 trials, some of which did not have the same inclusion criteria as this review, although 10 of the same trials were included in this report. The meta-analysis included Val-HeFT,[71] ELITE II,[88] and RESOLVD,[78] all three of which reported a slight but insignificant increase in mortality compared to the control group. The results of the CHARM-Overall program[70] were not included in the analysis where candesartan reduced all-cause mortality (borderline significance) in patients with HF. A meta-analysis of fair quality including patients with HF (published in 2000)[102] that only included trials using losartan was identified. It is difficult to draw any conclusions from the reduction in mortality, as the duration

of five of the six trials was 3 months or less and because of the small number of events in these trials.

More recently, a good quality meta-analysis of the angiotensin II receptor antagonists in patients with HF (and in patients with high-risk acute MI as discussed in Key Question 1 c),[66] evaluated 24 trials including over 38000 patients (17 of which were evaluated in this report). When compared to placebo, treatment with the angiotensin II receptor antagonists reduced all-cause mortality (OR 0.83 95% CI 0.69-1.00; P=0.048) and HF hospitalizations (OR 0.64 95% CI 0.53-0.78) in patients with HF. When a sensitivity analysis was performed excluding data from CHARM-Alternative, the difference in all-cause mortality was no longer statistically significant. There was not a difference in all-cause mortality or HF hospitalizations between treatment with an angiotensin II receptor antagonist compared to an ACEI. When evaluating combination therapy with an angiotensin II receptor antagonist and an ACEI compared to an ACEI alone, all-cause mortality was not reduced but there was a reduction in HF hospitalizations (OR 0.77 95% CI 0.69-0.87) with combination therapy.

Key Question 1e.

In patients with nephropathy, what is the comparative efficacy of different angiotensin II receptor antagonists in end-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance), or quality of life?

Summary

In patients with non-diabetic nephropathy, one active controlled trial reported the combination of losartan and trandolapril to reduce composite doubling sCr or ESRD compared to either treatment alone.[68] Another active-controlled trial reported the change in CrCl did not differ significantly with the combination of candesartan plus lisinopril compared to either monotherapy.[103] In one small trial of patients with non-diabetic nephropathy,[104] treatment with valsartan significantly decreased albuminuria compared to placebo. In another trial, the combination of valsartan and benazepril at half doses decreased the urinary protein excretion rate more than either drug alone at higher doses.[105] No conclusions as to the comparative efficacy of the angiotensin II receptor antagonists in patients with non-diabetic nephropathy can be made based on these trials.

Results from the three active-controlled trials in patients with diabetic nephropathy (one evaluating albumin excretion rate and GFR with valsartan vs. captopril vs. placebo,[106] another evaluating albuminuria with losartan and enalapril compared to placebo,[107] and another evaluating change in GFR at 5 years with telmisartan vs. enalapril[108]) did not help determine the comparative efficacy of the angiotensin II receptor antagonists in patients with diabetic nephropathy.

The angiotensin II receptor antagonists irbesartan and losartan reduced the composite doubling sCr, ESRD, or death in two large, placebo-controlled trials in patients with type 2 diabetic nephropathy.[109, 110] A subanalysis of CV outcomes in the trial with irbesartan,[111] and of patients with Asian ethnicity in the trial with losartan,[112] have been included in the update.

The outcome measures used in the two trials with irbesartan and losartan[109, 110] are well-accepted and considered to be measurements of hard clinical outcomes. The level of albuminuria is considered a surrogate marker, as the relationship to the progression to kidney failure and fatal CV events is not as well established. Variations in measurement have also made it difficult to compare results of clinical trials. The estimated GFR is preferred for estimating the level of chronic kidney disease.[113] It is recommended that sCr not be used alone to estimate the patient's level of kidney function, and the calculated CrCl is preferred to the use of sCr alone. It is unclear at this time how changes in these surrogate markers affect long-term clinical outcomes and research in this area is being encouraged.

As there were no head-to-head trials, additional data are needed before a definitive conclusion can be made as to the comparative efficacy of the angiotensin II receptor antagonists in patients with diabetic or non-diabetic nephropathy. From the results of two similarly designed trials, it appears that irbesartan and losartan are comparable in their effect on the composite outcome of doubling sCr, ESRD, and death in patients with diabetic nephropathy.

Head-to-head trials

We found no relevant head-to-head trials.

Active-controlled trials

Seven active-controlled trials were identified for analysis in patients with nephropathy and are presented in Evidence Table 7 and Quality Table 7. One trial included in the analysis was of good quality,[114] five trials were fair quality (due to inadequate description of method randomization and/or concealment, two were open-label, two trials did not include an intent-to-treat analysis, and one with a high drop-out rate)[103, 105, 107, 108] and one was poor quality[115] (due to a significant difference in diastolic BP and duration of DM at baseline, and not using an intent-to-treat analysis). Three of the trials evaluated an angiotensin II receptor antagonist compared to an ACEI, then compared to the combination: losartan vs. trandolapril vs. losartan plus trandolapril;[114] candesartan vs. lisinopril vs. candesartan plus lisinopril;[103] valsartan vs. benazepril vs. valsartan plus benazepril.[105] The other three trials were a comparison of valsartan vs. captopril vs. placebo,[106] losartan vs. enalapril vs. placebo,[107] and telmisartan vs. enalapril.[108] Four trials were excluded from the update due to wrong outcome.[116-119]

End-stage renal disease or deterioration of renal function

Combination treatment of an angiotensin-II receptor blocker and an angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE) was a randomized, double-blind, controlled trial[114] where the primary endpoint (composite doubling sCr or ESRD) occurred in 11% of patients on combination therapy and 23% of patients on losartan (HR 0.40 95% CI 0.17-0.69; P=0.016) and 23% of patients on trandolapril (HR 0.38 95% CI 0.18-0.63; P=0.018). The reduction in BP was similar for all treatment groups. A multicenter, randomized, open-label, controlled trial evaluated combination therapy in patients with non-diabetic nephropathy[103] and found no change in CrCl with combination candesartan plus lisinopril, a 7.7% decrease with candesartan, and a 2.4% decrease with lisinopril. The comparisons were not

statistically significant. In a small (n=24) single center, randomized, open-label cross-over trial in patients with nondiabetic nephropathies, the combination of valsartan with benazepril at half doses (e.g., valsartan 80mg, benazepril 10mg) reduced 24-hour urinary protein excretion rate (reduction of 56% vs. baseline) compared to either valsartan (reduction of 45.9%; P=0.024) or benazepril (reduction of 41.5%; P=0.002) alone[105] Due to the different endpoints and trial design, the effects of losartan, candesartan and valsartan in patients with non-diabetic renal disease cannot be compared.

In a multicenter, randomized, double-blind trial comparing two doses of valsartan with captopril in patients with diabetic nephropathy for 1 year,[106] there was a statistically significant decrease in albumin excretion rate with valsartan 80mg compared to placebo (P<0.05) as was captopril vs. placebo. The comparisons between valsartan and captopril were not statistically significant. The change in GFR was not statistically significant between groups.

In a randomized, double-blind, cross-over trial[107] of 16 patients with type 1 diabetic nephropathy, losartan 50mg and 100mg was compared to enalapril 10mg and 20mg or placebo for 2 months. Albuminuria was reduced by with both doses of losartan and both doses of enalapril (all P<0.05 vs. placebo). There was not a statistically significant difference between losartan 100mg and enalapril 20mg in the reduction in urinary albumin excretion rate. Glomerular filtration rate remained stable with all treatments. Blood pressures (24 hour SBP/DBP and mean arterial pressure) were reduced with all treatments vs. placebo (P<0.05) although there were no significant correlations between BP changes in each patient and albuminuria. From the results of this study, it is not possible to determine long-term benefit because of the 2-month treatment periods.

Valsartan appears to have a similar benefit to captopril, and losartan with enalapril, in patients with diabetic nephropathy, although the comparative renoprotective effect of these two agents cannot be determined from these two studies.

Treatment with telmisartan was reported to be noninferior to enalapril in 250 patients enrolled in the Diabetics Exposed to Telmisartan and Enalapril Study Group.[108] After analysis of 216 patients with baseline GFR and values at 5 years or using the last observation carried forward, the change in GFR was reported as -17.5 ml/min/$1.73m^2$ with telmisartan compared to -15.0 ml/min/$1.73m^2$ with enalapril; a treatment difference of -2.6ml/min/$1.73m^2$ (95% CI -7.6 to 2.0 ml/min/$1.73m^2$). It was concluded that telmisartan was noninferior to enalapril as the lower boundary of -7.6 was greater than the pre-defined value of -10.

Quality of life

None of the active-controlled trials evaluated quality of life in patients with nephropathy.

Placebo-controlled trials

Three placebo-controlled trials[104, 109, 110] were included for analysis in patients with nephropathy and are presented in Evidence Table 8 and Quality Table 8. Two trials included in the analysis were of good quality,[109, 110] and one was of fair quality (due to inadequate description of randomization and concealment and small patient population).[104] Two of the trials were in patients with type 2 diabetic nephropathy,[109, 110] and one in non-diabetic nephropathy.[104] Six trials were excluded due to wrong outcome[120-123,124,125]

The Irbesartan Type 2 Diabetic Nephropathy Trial (IDNT)[109] was a multicenter, randomized, double-blind trial evaluating the primary outcome of composite all-cause mortality,

doubling of sCr, and ESRD (defined as renal transplantation, initiation of dialysis, or sCr $\geq$ 6mg/dl) in 1715 patients with HTN, type 2 DM and nephropathy. Treatment with irbesartan 300mg once daily was compared to placebo or amlodipine 10 mg once daily for a mean follow-up of 2.6 years. The secondary CV endpoint included composite CV death, nonfatal MI, HF hospitalization, permanent neurologic deficit due to CVA, or lower limb amputation above the ankle. A subanalysis of CV outcomes in IDNT was also conducted.[111]

In the multicenter, randomized, double-blind Reduction of Endpoints in Patients with NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial,[110] losartan 50-100mg once daily (71% received a dosage of 100 mg once daily) was compared to placebo in 1513 patients with type 2 DM and nephropathy (with approximately 93% on antihypertensive medications) for a mean follow-up of 3.4 years. The primary endpoint was a composite of doubling of sCr, ESRD (need for chronic dialysis or renal transplantation), or death. The secondary endpoint of CV morbidity and mortality was a composite of MI, stroke, first hospitalization for HF or unstable angina, coronary or peripheral revascularization, or CV death. A subgroup analysis of the primary endpoint in 252 patients of Asian ethnicity enrolled in RENAAL has been included in the udpate.[112]

Nine patients were randomized to valsartan 80mg once daily or placebo in a double-blind trial of 6 months duration[104] evaluating albuminuria and GFR.

End-stage renal disease or deterioration of renal function

In IDNT,[109] the primary endpoint (composite doubling sCr, onset of ESRD, or all-cause mortality) was reported to be significantly reduced with irbesartan compared to patients on placebo (RR 0.80 95% CI 0.66-0.97, P=0.02; with the following calculated results based on crude rates of events: RRR from events 16.3%, RR 0.84 95% CI 0.72-0.98, ARR 6.4%, NNT=16 95% CI 8-119). The risk of the primary endpoint was also significantly reduced compared to treatment with amlodipine (P=0.006). When analyzed separately, doubling baseline sCr decreased with irbesartan vs. placebo (P=0.003) and vs. amlodipine (P<0.001). The decrease in ESRD and decrease in all-cause mortality with irbesartan was not statistically significant compared to placebo or amlodipine. The secondary composite CV endpoint was not statistically significant between irbesartan and placebo or amlodipine. Average mean arterial pressure (MAP) was 3.3 mm Hg lower in the irbesartan and amlodipine groups compared to placebo (P=0.001). The MAP was not significantly different between irbesartan and amlodipine. The CV subgroup analysis reported there was not a statistically significant difference in the composite CV outcome, CV death, MI, stroke, or cardiac revascularization with irbesartan compared to placebo. There was a significant reduction in HF favoring irbesartan over placebo (HR 0.72 95% CI 0.52-1.00, P=0.048) and compared to amlodipine (HR 0.65 95% CI 0.48-0.87, P=0.004).[111]

In RENAAL,[110] the primary endpoint (composite doubling sCr, onset of ESRD, or all-cause mortality) was statistically significantly reduced with losartan compared to placebo (RR 0.84 95% CI 0.72-0.98, P=0.02; calculated RRR from events 7.6%, calculated RR 0.92 95% CI 0.83-1.03, ARR 3.6%, NNT not calculable based on crude rates of events). When analyzed separately, doubling baseline sCr decreased with losartan vs. placebo (P=0.006) as did ESRD (P=0.002). The slight increase in all-cause mortality with losartan was not statistically significant (P=0.88). The secondary CV morbidity and mortality endpoint was not significantly different with losartan compared to placebo. At 1 year, MAP was 2.2 mm Hg lower in the losartan group (P<0.001) but was not significantly different at the end of the study. The decrease

in risk for the primary endpoint remained significant after adjustment for blood pressure. The primary endpoint was decreased in a subgroup of Asian patients, occurring in 41.9% of patients on losartan compared to 54.8% of patients on placebo (RRR 0.35 95% CI 0.07-0.55, P=0.02). There was not a statistically significant difference between treatment groups for the individual components of the primary endpoint (doubling sCr, ESRD, all-cause mortality), or the secondary endpoints of CV death, HF, MI, revascularization, unstable angina, or stroke in this patient population.[112]

A comparison of the results from IDNT and RENAAL is included in Table 6.

Table 6. Comparison of IDNT and RENAAL Trial Results

Trial	IDNT	RENAAL
Treatment (N)	Irbesartan 300 mg (579) Amlodipine 10 mg (567)* Placebo (569)	Losartan 50-100 mg (751) Placebo (762)
Mean Duration	2.6 years	3.4 years
Primary Endpoint	Composite doubling sCr, ESRD, death	Composite doubling sCr, ESRD, death
Results (Primary endpoint)	Irbesartan 189/579 (32.6%) Placebo 222/569 (39%)	Losartan 327/751 (43.5%) Placebo 359/762 (47.1%)
Relative risk reduction (RRR)	Irbesartan 20% (95% CI 3-34) P=0.02 (based on unadjusted relative risk)	Losartan 16% (95% CI 2-28) P=0.02 (based on Cox regression model)
Absolute risk reduction (ARR)	6.4% (based on crude rates of events)	3.6% (based on crude rates of events)
Calculated NNT	16 (95% CI 8-119)	-
Primary endpoint components (RRR)	Doubling sCr: 33% ↓ vs placebo (P=0.003) ESRD: 23% ↓ vs placebo (P=0.07) Death: 8% ↓ vs placebo (P=0.57)	Doubling sCr: 25% ↓ vs placebo (P=0.006) ESRD: 28% ↓ vs placebo (P=0.002) Death: 2% ↑ vs placebo (P=0.88)

* Results for amlodipine not shown

In the trial of nine patients with valsartan,[104] albuminuria was decreased with valsartan compared to placebo (P<0.05). The decrease in GFR seen with valsartan was not statistically significant compared to placebo.

Quality of life

None of the placebo-controlled trials in patients with nephropathy evaluated quality of life.

Systematic reviews

One good quality systematic review[54] was identified that evaluated the effect of the angiotensin II receptor antagonists compared to placebo or other antihypertensive therapy in patients with DM (previously discussed under Key Question 1a. in patients with HTN). Two of the trials discussed above (IDNT and RENAAL), and the substudy of LIFE in patients with DM were the only trials included in the systematic review and meta-analyses.[109, 110] The conclusion of the review was that antihypertensive therapy with an angiotensin II receptor antagonist in

patients with DM did not significantly reduce total mortality or CV morbidity and mortality. A statistically significant benefit was seen in reducing ESRD compared to placebo (OR 0.73 95% CI 0.60-0.89).

Key Question 2.

For adult patients with essential hypertension, high cardiovascular risk factors, recent myocardial infarction, heart failure, diabetic or nondiabetic nephropathy, do angiotensin II receptor antagonists differ in safety or adverse events?

Summary

The angiotensin II receptor antagonists appear to be well tolerated. Depending on the adverse effect, patient population, and agent evaluated, reports of adverse effects were similar to, increased, or decreased, compared to placebo. Withdrawal rates were generally less than placebo, except for studies in patients with HF. Withdrawals due to adverse events were also generally less than control treatment (typically compared to an ACEI). The incidence of adverse effects reported were similar to control, except for a lower frequency of cough compared to the ACEIs. In patients with a history of ACEI-induced cough, cough was reported in a slightly higher percent of patients than placebo but much lower than patients on an ACEI. Reports of angioedema are rare with the angiotensin II receptor antagonists, but have been reported to occur in patients previously experiencing angioedema on an ACEI.

There is not enough information to determine whether the angiotensin II receptor antagonists differ in adverse effects, withdrawals due to adverse events, or the incidence of serious adverse events in the different patient populations.

Overall adverse effect reports

There were no head-to-head trials in adult patients with essential hypertension, high CV risk factors, recent MI, HF, or diabetic or nondiabetic nephropathy, evaluating the outcomes specified in this report, in order to determine whether there is a difference in overall adverse effect reports between the angiotensin II receptor antagonists.

In active-controlled trials of good or fair quality included in this review, data on adverse effects were available regarding the use of candesartan, eprosartan, and losartan for patients with HTN, losartan and valsartan for patients with high CV risk factors, losartan and valsartan for patients with recent MI, candesartan, losartan, telmisartan, and valsartan for patients with HF, and candesartan, irbesartan, losartan, telmisartan, and valsartan for patients with nephropathy. Refer to Table 9 on adverse events in randomized controlled trials. No data were available for olmesartan from active-controlled trials for the specified outcomes.

Reported adverse effects of interest included hypotension (2-13.3%; 15.1% requiring dose reduction in one study),[62] dizziness (4.3-16.5%), and angioedema (0.1%-0.4%). Hyperkalemia was reported in 4.5% of patients in one trial,[114] requiring dose reduction in 1.3% of patients in another trial,[62] and requiring discontinuation in 0.6-1.9% of patients.[89, 109] Dose reduction due to renal causes was reported in 4.9% of patients in one trial.[62] Cough was reported in 2-9.3% of patients, with 12.8-16% in patients with a history of ACEI induced cough.[21, 22] The two trials in patients with HTN and a history of ACEI induced cough reported cough in 16% of

patients on candesartan, 31% on enalapril, and 11% of patients on placebo,[21] and 12.8% of patients on eprosartan, 28.2% on enalapril, and 7.3% of patients on placebo.[22]

For the placebo-controlled trials included in this review of good or fair quality, data were available with candesartan, irbesartan, and valsartan for patients with HTN, losartan for patients with high CV risk factors, losartan and valsartan for patients with recent MI, candesartan, irbesartan, losartan, and valsartan for patients with HF, losartan, and valsartan for patients with nephropathy. No data were available for telmisartan or olmesartan from placebo-controlled trials for the specified outcomes. Refer to Table 9 on adverse events in randomized controlled trials.

Reported adverse effects of interest included hypotension (14.7-24.6%; 0.5-4.5% requiring discontinuation), dizziness/light-headedness (8.6-26.1%; 1.6% requiring discontinuation), and angioedema (0.03-0.16%; up to 4.5% in one study of patients intolerant to an ACEI[87]). Discontinuations due to hyperkalemia were reported in 1.1-3.4% of patients. Discontinuations due to an increase in sCr or renal impairment were reported in 1.1-7.8% of patients.[67-71, 75, 87, 110] Doubling of sCr was reported in 5.5-6% of patients in two of the CHARM trials.[68, 69] In one study, cough was reported in 68.2% of HF patients with a history of ACEI induced cough.[87] Discontinuation due to cough was reported in 0.2% of patients in one study of patients with HF.[68]

No systematic reviews were available that compared the overall adverse effects of the different angiotensin II receptor antagonists.

In summary, the angiotensin II receptor antagonists appear to be well tolerated. The adverse effect profile of the angiotensin II receptor antagonists varied in that reports were similar to that of placebo in some clinical trials, whereas in others there was a significant increase or decrease compared to placebo, depending on the trial. The incidence of adverse effects reported were similar to control, except for a lower frequency of cough compared to ACEI controls. In patients with a history of ACEI induced cough, cough was reported in a slightly higher percent of patients than placebo but much lower compared to patients on an ACEI.

Withdrawals due to adverse events

There were no head-to-head trials in adult patients with essential hypertension, high CV risk factors, recent MI, HF, diabetic or nondiabetic nephropathy, evaluating the outcomes specified in this report, in order to determine whether there is a difference in withdrawals due to adverse events between the angiotensin II receptor antagonists.

In active-controlled trials of good or fair quality, overall withdrawal rates due to adverse events were generally less than control (losartan[20, 36] in patients with HTN, losartan[25] and valsartan[26] in patients at high CV risk, losartan[63] and valsartan[62] in patients with recent MI, telmisartan[108] and valsartan[106] in patients with nephropathy, and losartan[79-81, 86, 88, 89] and valsartan[83] in patients with HF). Withdrawal rates due to adverse events were higher than control in only a few trials (candesartan[21] in patients with HTN, and telmisartan[82] in patients with HF). It appears that losartan and valsartan are similar in withdrawal rates in patients with recent MI (compared to an ACEI). No data on overall withdrawals due to adverse events were reported for eprosartan or olmesartan in active-controlled trials of the specific outcomes evaluated in the report.

Withdrawal rates due to adverse events were generally less than placebo (candesartan[53] and irbesartan[38] in patients with HTN, losartan[110] in patients with nephropathy) except for patients with HTN on valsartan,[39] and on candesartan[67-70, 73, 87] and valsartan[74, 75] in patients with HF. No data were available for eprosartan, olmesartan, or telmisartan in the specified outcome

trials. Although difficult to compare the withdrawals rates for the angiotensin II receptor antagonists due to the differences in patient populations and trial design, data for candesartan and valsartan demonstrate a statistically significant reduction in withdrawal rates compared to placebo in the HF population.

No systematic reviews were available that compared the withdrawals due to adverse events of the different angiotensin II receptor antagonists.

In summary, the angiotensin II receptor antagonists appear to be well tolerated with a withdrawal rate due to adverse events less than control treatment in the majority of the trials (typically compared to an ACEI). Withdrawal rates were generally less than placebo, except for studies in patients with HF and one in HTN. No data were available for eprosartan or olmesartan from trials evaluated for the specified outcomes. No conclusions can be made as to whether the withdrawal rates due to adverse events differ between the angiotensin II receptor antagonists, as not enough data are available for all the agents in the different patient populations.

Serious adverse events reported (including mortality)

No head-to-head trials were available comparing the angiotensin II receptor antagonists and serious adverse events in the specified patient populations and outcomes.

Not all trials reported the incidence of serious adverse events. Serious adverse events and serious, drug-related adverse events were reported in 3.8% and 0.5% of patients, respectively, on losartan in a subgroup of patients without vascular disease in the LIFE trial.[56] Serious adverse events occurring more frequently with valsartan vs. control in the VALUE trial included angina (4.4%), atrial fibrillation (2.4%), and syncope (1.7%) (P<0.0001 for angina and syncope).[26]

In the placebo-controlled trials, serious adverse events were reported in 15.4% of patients with HTN on irbesartan, which was lower compared to placebo.[38] A placebo-controlled trial in patients with HF reported serious adverse events in 1.4%, 5.7%, and 5.6% of patients on candesartan 4mg, 8mg, and 16mg, respectively. Serious adverse events were reported in 4.7% of patients on placebo in this trial.[73] Death and CV events were evaluated as part of the safety analysis of one trial in patients with nephropathy. Stroke occurred in 5% vs. 4.6%, nonfatal MI in 7.5% vs. 4.6%, HF in 7.5% vs. 5.4%, and death in 5% vs. 4.6% of patients on telmisartan and enalapril, respectively.[108]

In the three systematic reviews and meta-analyses evaluated previously, mortality was not found to be significantly different from placebo or control therapy in patients with DM;[54] in patients with HF, mortality was not significantly different compared to control therapy,[101] but was reduced compared to placebo.[66]

In summary, there are not enough data to compare incidence of serious adverse events with the angiotensin II receptor antagonists. The effect of the angiotensin II receptor antagonists on all-cause mortality in patients with HF requires further study.

Specific adverse effects or withdrawals due to specific adverse events (e.g., renal impairment, cough, and angioedema)

There were no head-to-head trials evaluating specific adverse effects or withdrawals due to specific adverse events with the angiotensin II receptor antagonists.

Eight active-controlled trials of fair quality for adverse events (primarily due to statistical analysis for potential confounders not performed) were included that evaluated reports of a specific adverse effect with an angiotensin II receptor antagonist (refer to Evidence Table 10 and

Quality Tables 9 and 10 on studies of adverse events). Five of these trials evaluated the incidence of cough with losartan, telmisartan, or valsartan in patients with a history of ACEI-induced cough.[126-130] The three trials with losartan compared the incidence of cough to patients on lisinopril. In each of the trials the incidence of cough was reported to be lower with losartan compared to patients on lisinopril (18% vs. 97%, P<0.001[127]; 36.7% vs. 87.5%, P<0.001[130]; 29.2% vs. 71.7%[128]). Dry cough was reported in 15.6% of patients on telmisartan compared to 60% on lisinopril (P=0.004) and 9.7% on placebo. Frequency of dry cough on a Visual Analogue Scale was significantly higher in patients on lisinopril compared to telmisartan (P=0.0016).[129] There was also a significant difference in the incidence of cough reported in patients treated with valsartan (19.5%) compared to patients on lisinopril (68.9%) (P<0.001). Withdrawals due to cough occurred in one patient on valsartan.[126] One study compared eprosartan and enalapril on cough in unselected patients with HTN and reported a 5.4% incidence of definite cough at 12 weeks with enalapril compared to 1.5% with eprosartan, and 6.1% vs. 1.5% at 26 weeks, respectively. Seven patients in the enalapril group and 2 on eprosartan withdrew due to cough.[131] Two of the studies assessed the effect of valsartan on sexual function in comparison to a beta-adrenergic blocker by patient questionnaire.[36, 132] The difference in episodes of sexual intercourse with valsartan compared to baseline were not significant although the difference between carvedilol and valsartan was statistically significant, with patients reporting a higher number of episodes of sexual intercourse per month after 16 weeks of therapy.[36, 132]

One small crossover trial evaluated the incidence of hyperkalemia in patients with chronic renal insufficiency and a history of potassium $\geq$ 4 mEq/L during treatment with either an angiotensin II receptor antagonist or an ACEI. In this trial, there was a statistically significant increase in serum potassium seen with lisinopril compared to losartan (5.0$\pm$0.18 vs. 4.6$\pm$0.17mEq/L; P=0.005).[133]

None of the trials specifically evaluated the occurrence of renal impairment as an adverse effect. As reported in the section on overall adverse effects, discontinuations due to an increase in sCr or renal impairment were reported in 1.1-7.8% of patients on an angiotensin II receptor antagonist.[67-71, 75, 87, 110] Doubling of sCr was reported in 5.5-6% of patients in two of the CHARM trials.[68, 69]

Placebo-controlled trials were not available that were designed to evaluate a specific adverse effect or withdrawal due to specific adverse events. In the CHARM-Alternative trial,[68] over 70% of patients randomized to candesartan experienced previous intolerance to an ACEI due to cough. Cough was the reason for discontinuation in 0.2% of patients on candesartan compared to 0.4% patients on placebo. In the same trial,[68] 3 of 1013 patients randomized to candesartan experienced angioedema. None of these patients required hospitalization and only one required discontinuation of the drug (0.1%). All 3 cases occurred out of the 39 patients who previously experienced angioedema or anaphylaxis on an ACEI (7.7%). None of the 1015 patients who received placebo experienced angioedema.

Angioedema has been reported with the angiotensin II receptor antagonists but to a lesser degree than the ACEIs. The exact mechanism for this reaction is unknown. In ACEIs, angioedema is thought to be associated with bradykinin accumulation. The incidence of angioedema in patients taking ACEIs is approximately 0.1-1.2%. According to information from the manufacturer, angioedema was reported in less than 0.5% of patients treated with candesartan.[6] Facial edema has been reported in 5 patients receiving eprosartan.[8] Facial edema has also been reported with irbesartan and very rarely, angioedema, in post-marketing

experience.[9] Facial swelling was reported in < 1% of patients on losartan, and angioedema in one patient with known hypersensitivity to aspirin and penicillin who was participating in a study. During post-marketing experience, angioedema was rarely reported with losartan, with some of the patients having a previous reaction with other medications including ACEIs.[10] There have been five reports of facial edema with olmesartan.[11] One case of angioedema was reported in a total of 3,781 patients treated with telmisartan.[12] Angioedema with valsartan has been one of the less frequently reported adverse events in clinical trials and there have been rare reports during post-marketing experience.[13]

There were no systematic reviews available comparing the angiotensin II receptor antagonists for specific adverse effects or withdrawals due to specific adverse events. A meta-analysis of seven placebo-controlled trials evaluated the safety and efficacy of olmesartan in patients with HTN (fair quality for adverse events).[134] According to the safety analysis, 2.1% of patients on olmesartan withdrew due to adverse events compared to 1.1% of patients receiving placebo. Drug-related adverse events were reported in 26.9% on olmesartan and 22.0% of patients on placebo. Headache was the most common adverse event, occurring in 7.8% of patients on olmesartan and 9.4% on placebo. Serious adverse events (including angina, chest pain, MI) occurred in 2.0% and 1.4% of patients on olmesartan and placebo, respectively. The two deaths in over 3000 patients treated were thought to be unrelated to drug therapy.

One retrospective cohort study[135] (fair quality for adverse events) evaluated the occurrence of adverse events by survey of General Practitioners in England who wrote a prescription for valsartan that was dispensed by the National Health Service (refer to Evidence Table 10 and Quality Table 10). Surveys were sent out 6 months after the initial prescription and 14,127 surveys were returned (55% survey response rate). Adverse reactions were reported in 1.6% of the patients analyzed from 12,881 surveys. The most frequently reported event was unspecified side effects (0.4%). Dizziness was reported in 0.1% of the cohort. By 6 months, 19.9% had stopped taking valsartan. Angioneurotic edema was reported in 5 cases (0.03%) as the reason for discontinuing the drug. Three of these cases were reported in the first month of treatment.

We present in Table 7 the results of our pooled analyses of the occurrence of specific adverse events in placebo-controlled studies of angiotensin II receptor antagonists. By comparing the 95% confidence intervals for each point estimate, we can conservatively estimate whether the occurrence of these adverse events may differ between these drugs. These data support that there is an increased risk associated with various angiotensin II receptor antagonists use relative to placebo of hypotension, dizziness/vertigo, increased serum creatinine, and hyperkalemia; that there is no direct head-to-head evidence about the relative risk of any adverse event, and indirect evidence (based on non overlapping 95% CIs) supporting a stronger association with dizziness and vertigo for valsartan compared to placebo than any of the other angiotensin II receptor antagonists. However, this pooled result was due to a statistically significant difference in this outcome seen in only one trial[71] and therefore we do not judge these data as conclusive. In addition, trials in different patient populations with various disease states make it difficult to compare adverse event rates across studies. Direct, head-to-head trials would be needed to definitively assess this question.

Table 7. Occurrence of selected adverse events in placebo-controlled trials of angiotensin II receptor antagonists

Adverse Events	Drug	# of studies	Placebo # adverse events	Placebo sample size	Intervention Groups # adverse events	Intervention Groups sample size	Pooled OR	95% CI	Zelen p-values
Hypotension[53, 70, 73, 77, 87]	Candesartan	5	659	6705	807	7243	1.24	(1.10, 1.39)	< 0.0001
Hypotension	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Hypotension[97]	Irbesartan	1	0	52	7	57	Inf+	(1.4, Inf+)	NC
Hypotension	Losartan	0	NR		NR	NR	NC	NC	NC
Hypotension[39, 71, 72, 106]	Valsartan	4	31	2735	66	2788	2.15	(1.37, 3.45)	0.0756
Dizziness/Vertigo[53, 77]	Candesartan	2	497	2607	532	2628	1.08	(0.94, 1.24)	0.0301
Dizziness/Vertigo	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Dizziness/Vertigo[97]	Irbesartan	1	12	52	13	57	0.99	(0.37, 2.67)	NC
Dizziness/Vertigo	Losartan	0	NR	NR	NR	NR	NC	NC	NC
Dizziness/Vertigo[39, 71, 72, 106]	Valsartan	4	47	2735	88	2788	2.00	(1.35, 2.98)	0.0004
Increased sCr/Renal impairment[70, 73, 87]	Candesartan	3	129	4098	271	4615	1.98	(1.59, 2.47)	0.0083
Increased sCr/Renal impairment	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Increased sCr/Renal impairment	Irbesartan	0	NR	NR	NR	NR	NC	NC	NC
Increased sCr/Renal impairment[110]	Losartan	1	9	762	11	751	1.24	(0.47, 3.42)	NC
Increased sCr/Renal impairment[39, 71]	Valsartan	2	8	2525	31	2541	3.86	(1.73, 9.77)	0.0678
Cough[21, 87]	Candesartan	2	62	117	132	241	1.20	(0.71, 2.02)	0.2797
Cough[22]	Eprosartan	1	2	41	2	39	1.05	(0.07,15.23)	NC
Cough	Irbesartan	0	NR	NR	NR	NR	NC	NC	NC
Cough	Losartan	0	NR	NR	NR	NR	NC	NC	NC
Cough[106]	Valsartan	1	1	29	4	62	1.92	(0.18, 98.44)	NC
Hyperkalemeia[70, 87]	Candesartan	2	25	3887	95	3982	3.62	(2.30, 5.89)	0.0637
Hyperkalemeia	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Hyperkalemeia[109]	Irbesartan	1	2	569	11	579	5.48	(1.19, 51.14)	NC
Hyperkalemeia[110]	Losartan	1	4	762	8	751	2.04	(0.54, 9.30)	NC
Hyperkalemeia[39]	Valsartan	1	0	26	2	30	Inf+	0.16, Inf+)	NC
Bronchitis/flu/upper respiratory infection[53, 73]	Candesartan	2	405	2671	422	3110	0.99	(0.85, 1.15)	0.1341
Bronchitis/flu/upper respiratory infection	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Bronchitis/flu/upper respiratory infection	Irbesartan	0	NR	NR	NR	NR	NC	NC	NC
Bronchitis/flu/upper respiratory infection	Losartan	0	NR	NR	NR	NR	NC	NC	NC
Bronchitis/flu/upper respiratory infection[106]	Valsartan	1	0	29	0	62	NC[1]	NC	NC

Adverse Events	Drug	# of studies	Placebo		Intervention Groups		Pooled OR	95% CI	Zelen p-values
			# adverse events	sample size	# adverse events	sample size			
Nausea/Vomiting	Candesartan	0	NR	NR	NR	NR	NC	NC	NC
Nausea/Vomiting	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Nausea/Vomiting[97]	Irbesartan	1	11	52	3	57	0.21	(0.04, 0.86)	NC
Nausea/Vomiting[74]	Losartan	1	0	17	1	16	Inf+	(0.03, Inf+)	NC
Nausea/Vomiting[106]	Valsartan	1	1	29	1	62	1.02	(0.52, 2.01)	NC
Angioedema[70, 87]	Candesartan	2	7	3387	13	3982	1.26	(0.46, 3.82)	0.3191
Angioedema	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Angioedema	Irbesartan	0	NR	NR	NR	NR	NC	NC	NC
Angioedema	Losartan	0	NR	NR	NR	NR	NC	NC	NC
Angioedema	Valsartan	0	NR	NR	NR	NR	NC	NC	NC
Headache	Candesartan	0	NR	NR	NR	NR	NC	NC	NC
Headache	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Headache[97]	Irbesartan	1	6	52	11	57	1.82	(0.56, 6.54)	NC
Headache	Losartan	0	NR	NR	NR	NR	NC	NC	NC
Headache[106]	Valsartan	1	1	29	1	62	0.46	(0.01, 37.31)	NC
GI disorder/upset[87]	Candesartan	1	7	91	13	179	0.94	(0.33, 2.89)	NC
GI disorder/upset	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
GI disorder/upset	Irbesartan	0	NR	NR	NR	NR	NC	NC	NC
GI disorder/upset	Losartan	0	NR	NR	NR	NR	NC	NC	NC
GI disorder/upset[106]	Valsartan	1	0	29	1	62	Inf+	(0.01, Inf+)	NC

[1] Both groups report zero events. OR not calculcated.

OR: Odds Ratio
CI: Confidence Interval
NR: Not Reported
NC: Not Calculated
Inf+: Infinity (when there are zero events in the placebo group and > zero events in the treatment group)

In summary, in trials evaluating patients with previous ACEI-induced cough, the incidence of cough was similar to that seen with placebo in patients treated with candesartan, losartan, telmisartan, or valsartan, and was statistically significantly less than comparisons with an ACEI. In trials specifically evaluating cough as a side effect, the incidence of cough was less with patients on eprosartan compared to an ACEI. Reports of angioedema are rare with the angiotensin II receptor antagonists, and have occurred in patients previously experiencing angioedema on an ACEI. There are not enough data to be able to compare the differences in specific adverse effects of the angiotensin II receptor antagonists.

Key Question 3.

Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one angiotensin II receptor antagonist is more effective or associated with fewer adverse events (e.g., renal insufficiency)? Evidence unique to minority and ethnic groups are of particular interest.

<u>Summary</u>

The majority of patients enrolled in the trials were white men in their late 50's to early 70's. Despite the subgroup of black patients being a minority in the trials (1-22% of patients), some of these were very large trials allowing for subgroup analyses. Evaluation of the subgroup of black patients in two trials brought into question the efficacy of losartan in patients with HF or HTN and LVH with an increase in risk for morbidity and mortality.[10, 25, 58, 71] Additional information in the subgroup of black patients is needed with losartan and the other angiotensin II receptor antagonists to confirm or refute these findings. Anywhere from 6-64% of patients enrolled in the trials were women. It appears that women derive similar benefit as men, and age did not appear to have a significant impact on the results of the angiotensin II receptor antagonists studied. There are inadequate data to determine whether there is a difference between the angiotensin II receptor antagonists with respect to patient demographics.

Subgroup analyses by concomitant medical conditions did not establish a difference in benefit with losartan in the composite endpoint of CV death, MI, and stroke in patients with HTN and LVH, although there was a difference in the outcome based on subgroups of patients with DM and patients without vascular disease for the individual CV endpoints. There is not enough evidence with other angiotensin II receptor antagonists to determine whether comorbidities influence results or whether there is a difference between the agents in this class.

Conflicting results are available regarding the effect of an angiotensin II receptor antagonist in combination with an ACEI and beta-adrenergic blocker in patients with HF as data from a subgroup analysis with valsartan found an increase in mortality[71] whereas data with candesartan showed no difference in mortality, but a significant decrease in the combined endpoint of CV mortality and HF hospitalizations.[68]

Age

There were no head-to-head trials, active-controlled trials, or placebo-controlled trials that were designed to compare the safety or effectiveness of the angiotensin II receptor antagonists according to age.

Four of the trials included within study comparisons of age and the effect of the angiotensin II receptor antagonists. The results did not differ based on age in patients with HF[69-71, 77] or HTN.[19] Randomized controlled trials conducted with an angiotensin II receptor antagonist in older patients with hypertension showed that treatment with candesartan,[136, 137] eprosartan,[138] irbesartan,[115] or valsartan[139, 140] was effective in lowering blood pressure and well tolerated in this patient population. Subanalysis of elderly patients in outcome trials of patients with HTN[40] and HF[92] reported similar benefits in these age groups.

The average age of patients enrolled in the trials included in the review were 54-76 years for HTN (candesartan, eprosartan, losartan, valsartan), 65-67 (70 in a subgroup analysis) for high CV risk (candesartan, losartan, valsartan), 65-67 for recent MI (losartan, valsartan), 54-74 for HF (candesartan, irbesartan, losartan, telmisartan, valsartan) and 42-61 for nephropathy (candesartan, irbesartan, losartan, telmisartan, valsartan).

Racial Groups

There were no head-to-head trials, active-controlled trials, or placebo-controlled trials that were designed to compare the safety or effectiveness of the angiotensin II receptor antagonists according to racial group.

One trial included a within study comparison of race and the effect of the angiotensin II receptor antagonists in patients with HF.[71] In this trial, the relative risk of the primary endpoint of combined morbidity and mortality with valsartan was 1.11 (95% CI 0.77 to 1.61) in the 344 black patients (7% of the overall patient population) enrolled in the study. In another trial of patients at high CV risk,[25] in a subgroup analysis of black patients, the primary endpoint (CV death, nonfatal stroke, nonfatal MI) occurred in 11% on atenolol compared to 17% on losartan. Based on these findings the indication for losartan in reducing the risk of stroke in patients with HTN and LVH, includes clarification that refers to the evidence that this benefit does not apply to black patients.[10] A subgroup analysis of Asian patients with type 2 DM and nephropathy reported a significant reduction in the primary endpoint of doubling sCr, ESRD, and death, a benefit that was also seen in the overall patient population.[112]

As with the ACEIs, the angiotensin II receptor antagonists are considered to be not as effective in lowering blood pressure in black compared to nonblack patients, whereas this difference in efficacy appears to be negated with the addition of a diuretic.[2,141-143] A systematic review of the effect of various antihypertensive agents on blood pressure in black patients was conducted. Four placebo-controlled trials were included for the evaluation of the angiotensin II receptor antagonists. According to the results, treatment with an angiotensin II receptor antagonist was beneficial in reducing systolic (P<0.001) as well as diastolic BP (P<0.001) in black patients compared to placebo. Not enough data were available to pool results for morbidity and mortality outcomes.[144]

A controlled trial in patients with hypertension reported a significant increase in the incidence of cough with enalapril vs. eprosartan (5.4% vs. 1.5%, respectively) however, of the 40 black patients in a subgroup analysis, none of the patients in the eprosartan group and one patient on enalapril experienced cough related to the study drug.[145]

The incidence of angioedema in patients taking ACEIs is approximately 0.1-1.2%.[146] It has been reported that black patients have an increased relative risk of 4.5 of angioedema associated with use of an ACEI compared to white patients.[147] It is unknown whether this increased risk also applies to the angiotensin II receptor antagonists.

Overall, black patients were included as approximately 1-17% of the population in the outcome trials of patients with HTN, 6% of patients at high CV risk, 3% of those with recent MI, 1-22% of patients with HF, and 14-15% with nephropathy. Other patient populations represented in these trials were Hispanic and Asian, most included as 0.5-5% of patients, with one trial[110] including 18% Hispanic and 16% Asian patients, and another enrolling over 200 patients, 100% who were Japanese.[114]

Gender

There were no head-to-head trials, active-controlled trials, or placebo-controlled trials that were designed to compare the safety or effectiveness of the angiotensin II receptor antagonists according to gender. One randomized, controlled trial enrolling only women found candesartan to be effective in lowering blood pressure and treatment was well tolerated.[148]

Four of the trials included within study comparisons of gender and the effect of the angiotensin II receptor antagonists. The results were consistent regardless of gender in patients at high CV risk[57] and in patients with HF.[69,71,88,70] In one subgroup analysis of patients with HTN, gender did not have an effect on treatment outcomes.[40, 69, 71, 88]

Overall, the majority of patients enrolled in the trials included in this review were men although in some trials, the majority enrolled were women. The following trials enrolled women as the majority of the patient population: 54%[25] and 58%[26] of patients at high CV risk; 63%[21] and 54%[53] of patients with HTN; 53% of patients with nephropathy;[114] 51%,[74] 62%,[85] and 80%[75] of patients with HF. In the active-controlled and placebo-controlled trials, women were included as 41-64% of patients in the HTN trials, as 49-58% of patients at high CV risk, as approximately 30% of patients in the recent MI trials, as 6-62% of patients with HF (with one trial enrolling 21 patients including 80% women), and as 26-53% of patients with nephropathy.

Comorbidities

There were no head-to-head trials, active-controlled trials, or placebo-controlled trials that were designed to compare the safety or effectiveness of the angiotensin II receptor antagonists according to patient comorbidities.

One of the active-controlled trials in patients at high CV risk,[25] and one of the placebo-controlled trials in patients with HTN[53] evaluated subgroups of patients based on their comorbidities. The primary composite endpoint of CV morbidity and mortality was decreased in the patients at high CV risk receiving losartan in the subgroup of patients without vascular disease,[56] patients with DM,[57] and patients with ISH.[25] In the subgroup analysis of patients with HTN, the reduction in major CV events seen with candesartan was greater in patients with a previous stroke compared to patients without a history of stroke.[40] In another subgroup analysis of this same trial,[53] treatment with candesartan reduced the risk of stroke in patients with ISH.[41]

One trial evaluated the safety of an angiotensin II receptor antagonist in hypertensive patients with asthma and found that treatment with candesartan or a calcium channel blocker did not result in significant changes in incidence or frequency of chronic cough in either group.[149]

Two trials with losartan,[150, 151] one which was a head-to-head crossover comparison with irbesartan,[151] evaluated the effect of an angiotensin II receptor antagonist on serum uric acid in patients with asymptomatic[150] or symptomatic[151] hyperuricemia. Treatment with losartan resulted in a significant reduction in serum uric acid compared to placebo in hypertensive patients with thiazide-induced hyperuricemia.[150] In comparison with irbesartan, losartan significantly reduced serum uric acid levels however, the clinical significance of whether there is a difference in acute gout attacks over time could not be determined from this study.[151]

Other Medications

There were no head-to-head trials, active-controlled trials, or placebo-controlled trials that were designed to compare the safety or effectiveness of the angiotensin II receptor antagonists according to concomitant medications.

Four trials included within study comparisons of the effect of an angiotensin II receptor antagonist in patients receiving therapy with an ACEI in addition to a beta-adrenergic blocker,[67,71] or in patients treated with an angiotensin II receptor antagonist who were not on an ACEI.[68, 71, 77] Treatment with candesartan showed a beneficial effect in reducing CV death and HF hospitalizations[68] and valsartan in reducing combined morbidity and mortality[71] in patients with HF who are unable to tolerate an ACEI. The benefit of candesartan in decreasing progression of HF was seen regardless of treatment with or without an ACEI as well as with or without a beta-adrenergic blocker.[77] The evidence is not as clear for patients with HF who are receiving an ACEI and beta-adrenergic blocker, as adding an angiotensin II receptor antagonist suggested an increase in mortality in one trial with valsartan[71] whereas another trial with candesartan[68] did not show an increase (or decrease) in mortality but did show a reduction in CV death and HF hospitalization in patients on an angiotensin II receptor antagonist, ACEI, and beta-adrenergic blocker compared to patients not receiving an angiotensin II receptor antagonist. In patients with non-diabetic renal disease, one trial reported a reduction in combined doubling sCr and ESRD with the combination of losartan and trandolapril vs. either monotherapy.[114]

In vitro studies have demonstrated inhibition of the formation of irbesartan metabolites by cytochrome 2C9 substrates or inhibitors[9] and that cytochrome P450 2C9 and 3A4 are involved in the metabolism of losartan. Rifampin (an inducer of 3A4) decreased the AUC of losartan and its metabolite. Fluconazole (an inhibitor of 2C9) increased losartan AUC and decreased the AUC of the active metabolite. Telmisartan has some inhibition of CYP2C19, possibly inhibiting the metabolism of drugs metabolized by CYP2C19, but the clinical significance of this is unknown. Eprosartan, and olmesartan are not metabolized by the cytochrome P450 enzyme system and valsartan does not appear to be metabolized by this enzyme system.[9] Candesartan is also not significantly metabolized by this enzyme system. According to the manufacturer, telmisartan has been shown to increase peak and trough digoxin levels by 49% and 20%, respectively, based on a study in healthy volunteers.[12] In a subgroup analysis of digoxin levels in patients participating in the REPLACE trial,[152] the change in digoxin levels ranged from –0.1 to +0.6nmol/L. The manufacturer recommends monitoring trough digoxin levels at steady-state in patients receiving digoxin in conjunction with telmisartan.[12] Concomitant therapy with potassium sparing diuretics or potassium supplements may increase potassium in patients receiving the angiotensin II receptor antagonists. There are no head-to-head trials evaluating the rates of drug interactions with the AIIRAs.

SUMMARY AND DISCUSSION

Results of the key questions are summarized in Tables 8 and 9. The key questions concerned comparisons of efficacy and risks of the angiotensin II receptor antagonists. Strong conclusions are supported by results of efficacy and safety compared in head-to-head trials, however none have been published. Strong conclusions could still be supported by unequivocal, consistent evidence from trials that compare the different angiotensin II receptor antagonists to a common comparator, generally placebo. In such cases, indirect measures of comparative efficacy may be justified. However, we did not find unequivocal, consistent evidence, and therefore no strong conclusions can be made about the differential efficacy and risks among the angiotensin II receptor antagonists.

Table 8. Summary of the Evidence by Key Question

Key Question 1: Efficacy	Quality of Evidence	Conclusion
HTN: comparative efficacy on all-cause and CV mortality, CV events (stroke, MI, or development of HF), ESRD (including dialysis or need for transplantation) or clinically significant or permanent deterioration of renal function (increase in sCr or decrease in CrCl), or QOL	Fair (candesartan: morbidity and mortality endpoints, QOL; irbesartan: renal endpoints; losartan: renal endpoints, QOL; eprosartan: morbidity and mortality, QOL) Poor (candesartan: QOL)	No head-to-head trials comparing AIIRAs in HTN. **Candesartan** (one placebo-controlled trial with open-label antihypertensive therapy with subanalyses) did not reduce composite major CV events or total mortality in older patients with HTN but did reduce non-fatal stroke compared to active control; reduction in first stroke seen in subgroup analysis ISH; decrease first CV event in subgroup patients with stroke. Candesartan (one active-controlled trials) improved one parameter of QOL compared to placebo in patients with ACEI-induced cough. **Eprosartan** (one active-controlled trial) reduced combined primary endpoint of cerebrovascular and CV events and nonCV death in patients with HTN and a previous cerebrovascular event, compared to nitrendipine; (two active-controlled trials) did not demonstrate improved QOL compared to placebo or control. **Irbesartan** 300mg (one placebo-controlled trial) reduced time to onset diabetic nephropathy vs. placebo in patients with HTN and type 2 DM with microalbuminuria (reduction with irbesartan 150mg not significant vs. placebo). UAE level significantly decreased in combined irbesartan groups vs. placebo. Restoration of normoalbuminuria was significantly superior in patients on irbesartan 300mg vs. placebo. Change in CrCl was not significantly different between groups. **Losartan** (one active-controlled trial) improved GFR compared to baseline and decreased symptom bother due to cough compared to enalapril; (one active-controlled trial) improved QOL compared to baseline and control. **Valsartan** (one placebo-controlled trial) did not result in significant change in GFR vs. placebo. Comparisons between the AIIRAs on QOL could not be made.
High CV Risk: comparative efficacy of different AIIRAs in all-cause and CV mortality, CV events (stroke, MI, or development of HF), or QOL	Good (valsartan) Fair (losartan) Poor (candesartan)	No head-to-head trials comparing AIIRAs in high CV risk. **Losartan** (one active-controlled trial) reduced CV morbidity and mortality compared with atenolol in patients with HTN and LVH. The benefit was largely due to the reduction in stroke. The benefit does not appear to apply to black patients. Losartan (four active-control substudies vs. atenolol): without vascular disease: reduced combined CV morbidity and mortality and stroke; ISH: reduced combined CV morbidity and mortality, all-cause mortality, CV mortality, stroke; DM: reduced combined CV morbidity and mortality, all-cause mortality, CV mortality, HF hospitalizations; Black patients: CV morbidity and mortality, stroke increased with losartan compared to atenolol. **Valsartan** (one active-controlled trial) did not differ in CV morbidity and mortality compared to amlodipine in patients with HTN at high CV risk.
Recent MI: comparative efficacy of AIIRAs in all-cause and CV mortality, CV events (usually, development of HF), or QOL	Good (losartan, valsartan)	No head-to-head trials comparing AIIRAs in recent MI. **Losartan** (one active-controlled trial) unable to conclude whether treatment is not superior or non-inferior to captopril in reducing all-cause mortality in a similar patient population. **Valsartan** (one active-controlled trial) is not inferior to captopril in reducing all-cause mortality, CV mortality, and other CV endpoints in high-risk patients with recent MI; treatment with valsartan in combination with captopril did not provide additional benefit.

Key Question 1: Efficacy	Quality of Evidence	Conclusion
HF: comparative efficacy of AIIRAs in all-cause and CV mortality, symptomatic improvement (HF class, functional status, visual analogue scores, exercise tolerance), hospitalizations for HF, or QOL	Good (morbidity/mortality: candesartan, losartan, valsartan) Fair (symptoms/QOL: candesartan, irbesartan, losartan, telmisartan, valsartan) Poor (symptoms: irbesartan)	There were no head-to-head trials comparing AIIRAs in patients with HF. **Candesartan** (three placebo-controlled trials with two pooled analyses) reduced CV death and HF hospitalizations (including patients on an ACEI and beta-blocker and those who were ACEI intolerant). Overall, there was no significant effect on mortality; in the pooled analysis of patients with low LVEF, there was a significant reduction in all-cause mortality. Also improved symptoms of HF (two placebo-controlled trials, one active-controlled trial), slowed progression HF (one placebo-controlled trial), and improved QOL (one placebo-controlled trial), and QOL and exercise tolerance (one active-controlled trial). **Irbesartan** (one placebo-controlled trial) improved exercise capacity compared to baseline but not statistically significant vs. placebo. **Losartan** did not reduce mortality or CV endpoints compared with an ACEI in patients with HF (one active-controlled trial, designed to evaluate results from another active-controlled trial showing benefit in secondary endpoint) but did improve symptoms of HF and QOL (four active-controlled trials, two placebo-controlled trials). **Valsartan** (two placebo-controlled trials) reduced combined morbidity and mortality, and hospitalization in a subanalysis, in patients with HF but increased mortality in patients on combination with an ACEI and beta-blocker in a subgroup analysis. Improved symptoms of HF and QOL (one active-controlled trial). Improved symptoms compared to ACEI control in patients not on a beta-blocker (one active-controlled trial). **Telmisartan** (one active-controlled trial) improved symptoms of HF similar to an ACEI but QOL results were difficult to assess.
Nephropathy: comparative efficacy of AIIRAs in ESRD (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in sCr or decrease in CrCl), or QOL	Good (irbesartan: doubling sCr, ESRD; losartan: doubling sCr, ESRD; telmisartan: GFR) Fair (candesartan: CrCl; losartan: albuminuria; valsartan: AER, albuminuria)	No head to head trials comparing AIIRAs in nephropathy. **Candesartan** (one active-controlled trial) reduction in CrCl not significant vs. lisinopril or combination in patients with non-diabetic nephropathy. **Irbesartan** (one placebo-controlled trial) reduced composite doubling sCr, onset of ESRD, or all-cause mortality compared to placebo or amlodipine in patients with diabetic nephropathy. When analyzed separately, only doubling baseline sCr decreased significantly with losartan vs. placebo. No significant difference in ESRD or all-cause death, or in a subanalysis of CV events. **Losartan** (one active-controlled trial) in combination with trandolapril, decreased composite doubling sCr or ESRD compared to either treatment alone in patients with non-diabetic nephropathy. Losartan (one active-controlled trial) reduced albuminuria compared to placebo (no significant difference in comparison with enalapril) in patients with diabetic nephropathy. Losartan (one large, placebo-controlled trial) reduced composite doubling sCr, onset of ESRD, or all-cause mortality compared to placebo in patients with diabetic nephropathy. When analyzed separately, only doubling baseline sCr and ESRD were decreased significantly with losartan vs. placebo. No significant difference in all-cause death. **Telmisartan** (one active-controlled trial) reported to be noninferior to enalapril in change in GFR in patients with type 2 DM and nephropathy. **Valsartan** (one active-controlled trial) decreased AER (with 80mg but not 160mg) compared to placebo (no significant difference between valsartan and captopril) in patients with diabetic nephropathy. Valsartan in combination with an ACEI at half doses (one active-controlled trial) reduced urinary protein excretion rate compared to either drug alone (at higher doses). Valsartan (one placebo-controlled trial) decreased albuminuria compared to placebo in small number of patients with non-diabetic nephropathy.

Key Question 2: Safety	Quality of Evidence	Conclusion
Adverse effects/events or withdrawals due to adverse effects or events	Fair	The AIIRAs appear to be well tolerated. Not enough data are available to determine whether the AIIRAs differ in adverse effects, withdrawals due to adverse events, or the incidence of serious adverse events in the different patient populations.
Key Question 3: Subgroups	**Quality of Evidence**	**Conclusion**
Age	Fair (eprosartan; subgroup analyses: candesartan; losartan; valsartan)	There does not appear to be a difference in results from individual AIIRAs based on age. There are inadequate data to determine whether one AIIRA is superior for a particular age group.
Gender	Fair (subgroup analyses: candesartan; losartan; valsartan)	There does not appear to be a difference in results from individual AIIRAs based on gender. There are inadequate data to determine whether one AIIRA is superior based on gender.
Race	Fair (subgroup analyses: candesartan; losartan; valsartan)	Losartan may not be as effective in black vs. non-black patients with HF or those with HTN and LVH and may increase morbidity and mortality (subgroup analyses). Additional information in the subgroup of black patients is needed with losartan and the other AIIRAs to confirm these findings. Subgroup analysis of Asian patients with type 2 DM and nephropathy appear to have similar results in the primary endpoint as the overall patient population. There are inadequate data to determine whether there is a difference between the AIIRAs.
Comorbidities	Fair (subgroup analyses: losartan)	The subgroup of patients with DM (with HTN and LVH) on losartan had a reduction in CV mortality but not a significant decrease in stroke as compared to the larger patient population. There is not enough evidence with other AIIRAs to determine whether comorbidities influence results. There are inadequate data to determine whether there is a difference between the AIIRAs.
Other medications	Fair (subgroup analyses: candesartan; valsartan)	The role of an AIIRA in combination with an ACEI and beta-blocker in patients with HF is unclear. Valsartan increased mortality whereas candesartan decreased CV mortality and HF hospitalizations in subgroup analyses of patients on combination with an AIIRA, ACEI, and beta-blocker. There are inadequate data to determine whether there is a difference between the AIIRAs.

Table 9. Summary of the Evidence by Drug and Condition

	HTN	High CV Risk	Recent MI	HF	Nephropathy
Candesartan	Reduced non-fatal stroke; some improvement in QOL	NA	NA	Reduced CV death and HF hospitalization (in patients on ACEI and beta-blocker and those ACEI intolerant); no significant effect on mortality except in low LVEF analysis; improved HF symptoms and QOL, and slowed HF progression	Decrease in CrCl not significant vs. ACEI or combination
Eprosartan	Reduced combined cerebrovascular and CV events and nonCV death; no improvement in QOL	NA	NA	NA	NA
Irbesartan	Reduced onset diabetic nephropathy (300mg)	NA	NA	Improved exercise capacity vs. baseline but not compared to placebo	Type 2 DM nephropathy: Reduced composite doubling sCr, ESRD, all-cause mortality; only doubling baseline sCr significant vs. placebo when analyzed separately
Losartan	Improved QOL	Reduced CV morbidity and mortality; reduced stroke	Unable to determine effect on mortality compared to ACEI	No reduction in mortality or CV endpoints compared with ACEI; improved HF symptoms and QOL	Type 2 DM nephropathy: Reduced composite doubling sCr, ESRD, all-cause mortality (only doubling baseline sCr and ESRD significant when analyzed separately); reduced albuminuria Non-DM nephropathy: Reduced doubling sCr, ESRD in combination w/ACEI
Olmesartan	NA	NA	NA	NA	NA
Telmisartan	NA	NA	NA	Improved symptoms	Type 2 DM nephropathy: noninferior to ACEI in change in GFR

| Valsartan | No difference in change in GFR | No difference in CV morbidity and mortality vs. DHP CCB | Reduced total mortality, CV mortality and CV events similar to ACEI | Reduced combined morbidity and mortality (in subgroup analysis, increased mortality in combination with ACEI and beta-blocker); improved HF symptoms and QOL | DM nephropathy: Reduced AER; Non-DM nephropathy: Reduced albuminuria |

* NA=data not available

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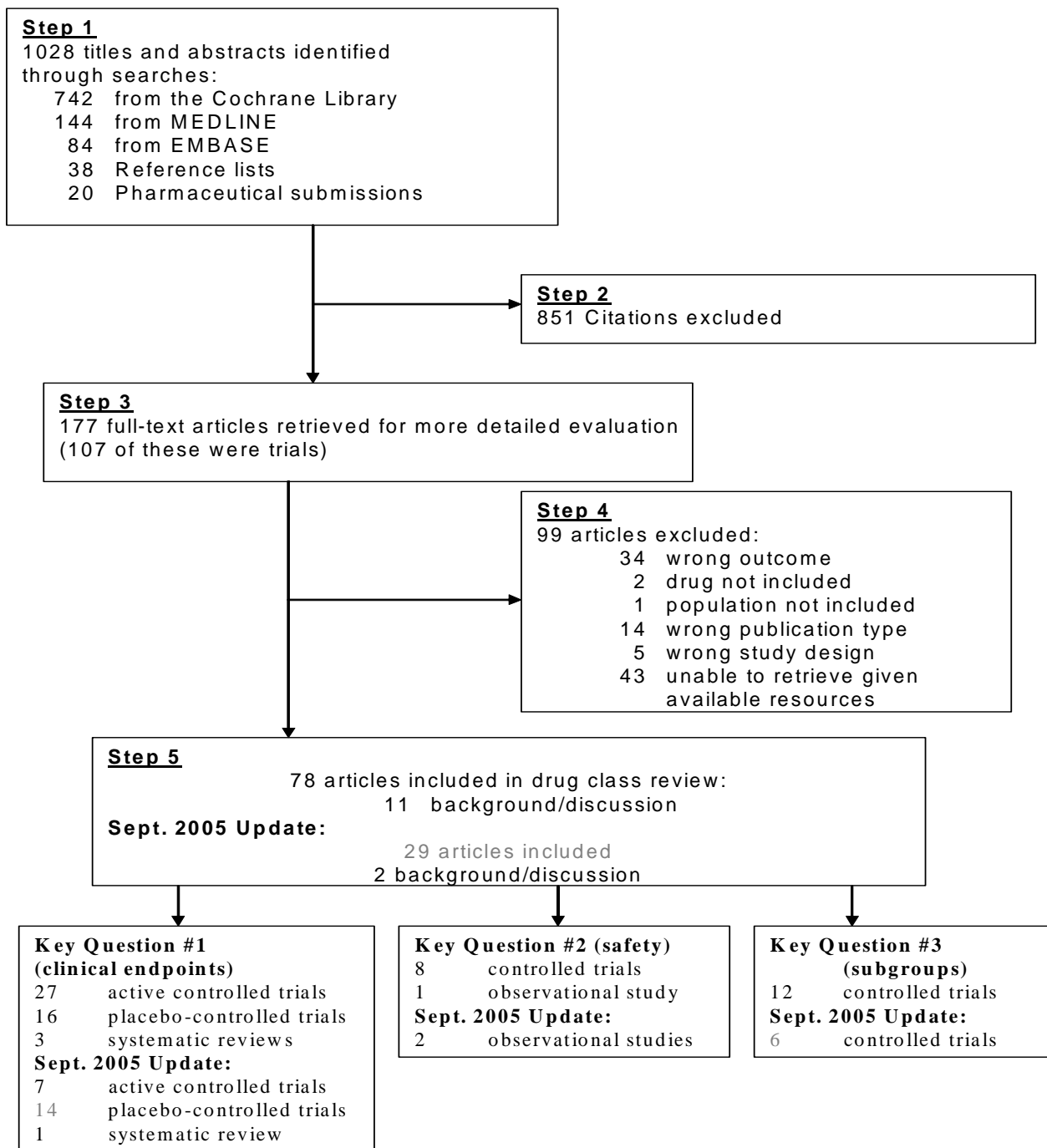
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Figure 1. Results of Literature Search

Step 1
1028 titles and abstracts identified
through searches:
   742 from the Cochrane Library
   144 from MEDLINE
    84 from EMBASE
    38 Reference lists
    20 Pharmaceutical submissions

Step 2
851 Citations excluded

Step 3
177 full-text articles retrieved for more detailed evaluation
(107 of these were trials)

Step 4
99 articles excluded:
    34 wrong outcome
     2 drug not included
     1 population not included
    14 wrong publication type
     5 wrong study design
    43 unable to retrieve given
           available resources

Step 5
78 articles included in drug class review:
    11 background/discussion
Sept. 2005 Update:
    29 articles included
  2 background/discussion

Key Question #1
(clinical endpoints)
27   active controlled trials
16   placebo-controlled trials
3   systematic reviews
Sept. 2005 Update:
7   active controlled trials
14   placebo-controlled trials
1   systematic review

Key Question #2 (safety)
8   controlled trials
1   observational study
Sept. 2005 Update:
2   observational studies

Key Question #3
    (subgroups)
12   controlled trials
Sept. 2005 Update:
6   controlled trials

Appendix A. AIIRA UPDATE 1 – SEARCH METHODOLOGY

EXPLANATORY NOTES:
In OVID databases, "mp" after a term or group of terms indicates a search of the following fields - title, original title, abstract, MESH headings, heading words, keyword
In OVID, the abbreviation "exp" indicates an "exploded" MESH term
In Embase an exclamation point indicates an "exploded" MESH term
In Embase, a question mark indicates truncation
In Embase, parentheses between words indicates a search of these words adjacent to one another – e.g. "high()blood()pressure." All text fields are searched, including title, abstract, and MESH headings.

DATABASE SEARCHED:
Cochrane (EBM Reviews Database on OVID)

TIME PERIOD COVERED: 2003-2005

SEARCH TERMS:
(losartan OR cozaar OR telmisartan OR micardis OR candesartan OR atacand OR eprosartan OR tevetan OR irbesartan OR avapro OR olmesartan OR benicar OR valsartan OR diovan).mp.

NUMBER OF ITEMS RETRIEVED: 290

===

DATABASE SEARCHED:
Medline (on OVID)

TIME PERIOD COVERED: 2003-2005

SEARCH TERMS:
losartan OR cozaar OR telmisartan OR micardis OR candesartan OR atacand OR eprosartan OR tevetan OR irbesartan OR avapro OR olmesartan OR benicar OR valsartan OR diovan
AND
congestive heart failure.mp. or exp Heart Failure, congestive/ OR hypertension/ OR high blood pressure.mp. OR diabetes mellitus.mp. OR exp Diabetes Mellitus/ OR myocardial infarct$.mp. OR exp Myocardial Infarction/
AND
randomized controlled trials/ OR rct.mp. OR systematic review$.mp.

NUMBER OF ITEMS RETRIEVED: 115

===

DATABASE SEARCHED:
Embase

TIME PERIOD COVERED: 2003-2005

OTHER LIMITERS:
ENGLISH
HUMAN

SEARCH TERMS:
losartan OR cozaar OR telmisartan OR micardis OR candesartan OR atacand OR eprosartan OR tevetan OR irbesartan OR avapro OR olmesartan OR benicar OR valsartan OR diovan
AND
congestive()heart()failure OR congestive heart failure! OR hypertension/de OR high()blood()pressure OR diabetes()mellitus OR diabetes mellitus! OR myocardial()infarct? OR myocardial infarction! OR heart infarction!
AND
randomized controlled trials! OR randomized()controlled()trial? OR rct OR randomized controlled trial! OR systematic()review? OR practice()guideline? OR practice guideline OR multicenter()study OR multi(2w)center()study OR multicenter study! OR controlled()clinical()trial?
AND
adult/de or aged/de

NUMBER OF ITEMS RETRIEVED: 275

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid.   A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
Adequate approaches to sequence generation:
        Computer-generated random numbers
        Random numbers tables
Inferior approaches to sequence generation:
        Use of alternation, case record numbers, birth dates or weekdays
    Not reported

2. Was the treatment allocation concealed?
    Adequate approaches to concealment of randomization:
        Centralized or pharmacy-controlled randomization
        Serially-numbered identical containers

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

Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days

Open random numbers lists

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

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of

study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

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

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

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

5. Are the primary studies summarized appropriately?

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

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

Appendix C. AIIRA Update 1 Articles

KQ=Key Question;
ACT=active-controlled trial;
PCT=placebo-controlled trial

Included
KQ #1 (HTN – ACT)
Schrader J, Lüders S, Kulschewski A, et al., for the MOSES Study Group. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention. Principal results of a prospective randomized controlled study (MOSES). Stroke 2005;36:1218-26.
Rec #: 2043
Notes: Public Comments

KQ #1 (HTN – PCT)
Degl'Innocenti A, Elmfeldt D, Hofman A, et al. Health-related quality of life during treatment of elderly patients with hypertension: results from the Study on COgnition and Prognosis in the Elderly (SCOPE). J Hum Hypertens 2004;18(4):239-45.
Rec #: 2002
Notes: Cochrane Central database. Using Smart Source Parsing
Apr

KQ #1 (HTN - PCT)
Papademetriou V, Farsang C, Elmfeldt D, et al., for the SCOPE Study Group. Study on, Cognition and Prognosis in the Elderly study, group. Stroke prevention with the angiotensin II type 1-receptor blocker candesartan in elderly patients with isolated systolic hypertension: the Study on Cognition and Prognosis in the Elderly (SCOPE). J Am Coll Cardiol 2004;44(6):1175-80.
Rec #: 2007
Notes: Cochrane Central database. Using Smart Source Parsing
2004 Sep

KQ #1 (HTN – PCT)
Faulhaber HD, Mann JF, Stein G, et al. Effect of valsartan on renal function in patients with hypertension and stable renal insufficiency. Curr Ther Res 1999;60(3):170-83.
Rec #: 2031

Pulled from Dossier
KQ #1 (HTN – PCT)
Yamamoto S, Kawashima T, Kunitake T, Koide S, Fujimoto H. The effects of replacing dihydropyridine calcium-channel blockers with angiotensin II receptor blocker on the quality of life of hypertensive patients. Blood Press Supplement 2003;2:22-8.
Rec #: 2019
Notes: Cochrane Central database. Using Smart Source Parsing
pp. Dec

KQ #1 (HTN – PCT); KQ #3 (demographic and comorbidity subgroups)
Trenkwalder P, Elmfeldt D, Hofman A, et al. The Study on COgnition and Prognosis in the Elderly (SCOPE) - major CV events and stroke in subgroups of patients. Blood Press 2005;14(1):31-7.
Rec #: 2033
PMID: 15823945
Notes: Embase database

KQ #1 (CV risk – ACT); KQ #3 (race subgroup)
Julius S, Alderman MH, Beevers G, et al. Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy: the LIFE study. J Am Coll Cardiol 2004;43:1047-55.
Rec #: 2000 (replaced reference 48 in Report with this citation)
Notes: Cochrane Central database. Using Smart Source Parsing
2004 Mar

KQ #1 (CV risk – ACT)
Kondo J, Sone T, Tsuboi H, et al. Effects of low-dose angiotensin II receptor blocker candesartan on cardiovascular events in patients with coronary artery disease. Am Heart J 2003; 146(6).
Rec #: 2018
Notes: Cochrane Central database. Using Smart Source Parsing
E20, Dec

KQ #1 (CV risk – ACT)
Julius S, Kjeldsen SE, Weber M, et al. for the VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004; 363(9426):2022-31.
Rec #: 2027
Notes: Cochrane Central database. Using Smart Source Parsing
Jun

KQ #1 (CV risk – ACT; Research Letter, not in evidence table)
Weber MA, Julius S, Kjeldsen SE, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial.[see comment]. Lancet 2004; 363(9426):2049-51.
Research Letter
Rec #: 2028
Notes: Medline database. Using Smart Source Parsing
Jun 19

KQ #1 (HF – ACT)
Little WC, Wesley-Farrington DJ, Hoyle J, et al. Effect of candesartan and verapamil on exercise tolerance in diastolic dysfunction. J Cardiovasc Pharmacol 2004;43(2):288-93.
Rec #: 2001
Notes: Cochrane Central database. Using Smart Source Parsing
Feb

KQ #1 (HF – ACT)
Kasama S, Toyama T, Kumakura H, et al. Addition of valsartan to an angiotensin-converting enzyme inhibitor improves cardiac sympathetic nerve activity and left ventricular function in patients with congestive heart failure. J Nucl Med 2003;44(6):884-90.
Rec #: 2010
Notes: Cochrane Central database. Using Smart Source Parsing
Jun

KQ #1 (HF – PCT)
Blanchet M, Sheppard R, Racine N, et al. Effects of angiotensin-converting enzyme inhibitor plus irbesartan on maximal and submaximal exercise capacity and neurohumoral activation in patients with congestive heart failure. Am Heart J 2005 May;149(5):e1-7.
Rec #: 2034
Embase Database

KQ #1 (HF – PCT)
Carson P, Tognoni G, Cohn JN. Effect of Valsartan on hospitalization: results from Val-HeFT. J Cardiac Fail 2003;9(3):164-71.
Rec #: 2017
Notes: Cochrane Central database. Using Smart Source Parsing
Jun

KQ #1 (HF - PCT)
Matsumori A, on behalf of the Assessment of Response to Candesartan in Heart Failure in Japan (ARCH-J) Study Investigators. Efficacy and safety of oral candesartan cilexetil in patients with congestive heart failure. Eur J

Heart Fail 2003;5(5):669-77.
Rec #: 2020
Notes: Cochrane Central database. Using Smart Source Parsing
Oct

        KQ #1 (HF – PCT); KQ #3 (elderly subgroup) Article pulled from Dossier
        Baruch L, Glazer RD, Aknay N, et al. Morbidity, mortality, physiologic and functional parameters in
elderly and non-elderly patients in the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 2004;148(6):951-7.
Rec #: 2030
Pulled from Dossier

        KQ #1 (HF - PCT)
        Young JB, Dunlap ME, Pfeffer MA, et al., for the Candesartan in Heart failure Assessment of Reduction in
Mortality and morbidity (CHARM) Investigators and Committees. Mortality and morbidity reduction with
candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM
low-left ventricular ejection fraction trials. Circulation 2004;110:2618-26.
Rec #: 2046
Notes: Public Comments

        KQ #1 (HF - PCT)

        O'Meara E, Lewis E, Granger C, et al. Patient perception of the effect of treatment with candesartan in
heart failure. Results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
(CHARM) programme. Eur J Heart Fail 2005;7:650-6.
Rec #: 2042
Notes: Public Comments

        KQ #1 (HF - PCT)

        O'Meara E, Solomon S, McMurray J, et al. Effect of candesartan on New York Heart Association
functional class. Results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
(CHARM) programme. Eur Heart J 2004;25:1920-6.
Rec #: 2047
Notes: Public Comments

        KQ #1 (Recent-MI and HF- meta-analysis)
        Lee VC, Rhew DC, Dylan M, et al. Meta-analysis: angiotensin-receptor blockers in chronic heart failure
and high-risk acute myocardial infarction. Ann Intern Med 2004;141:693-704.
Rec #: 2037
Pulled from Content Expert files

        KQ #1 (Nephropathy – ACT)
        Barnett AH, Bain SC, Bouter P, et al., for the Diabetics Exposed to Telmisartan and Enalapril Study Group.
Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J
Med 2004;351(19):1952-61. Corrections N Engl J Med 2005;352(16):1731.
Rec #: 2024
Notes: Cochrane Central database. Using Smart Source Parsing
2004 Nov

        KQ #1 (Nephropathy – PCT); KQ #3 (race subgroup)
        Chan JCN, Wat NMS, So WY, et al., on behalf of the Asian RENAAL Study Investigators. Renin
angiotensin aldosterone system blockade and renal disease in patients with type 2 diabetes. An Asian perspective
from the RENAAL Study. Diabetes Care 2004;27(4):874-9.
Rec #: 2005
Notes: Cochrane Central database. Using Smart Source Parsing
Apr

KQ #1 (Nephropathy – PCT)
Berl T, Hunsicker LG, Lewis JB, et al., for the Collaborative Study Group. Irbesartan Diabetic Nephropathy Trial. Collaborative Study, Group. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. Ann Intern Med 2003;138(7):542-9.
Rec #: 2013
Notes: Cochrane Central database. Using Smart Source Parsing
Apr

KQ #1 (Nephropathy - Summary)
Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
Rec #: 2038
Pulled from Content Expert files

KQ #2 (Safety)
Püchler K, Laeis P, Stumpe KO. Blood pressure response, but not adverse event incidence, correlates with dose of angiotensin II antagonist. J Hypertens 2001;19(suppl 1):S41-8.
Rec #: 2039
Reference Mining

KQ #2 (Safety)
Zanabli Ar, Yango A. Dworkin L. Incidence of hyperkalemia in high risk patients during treatment with an angiotensin converting enzyme inhibitor (Lisinopril) versus an angiotensin II receptor blocker (Losartan). S Dakota J Med 2004;57(6):227-31.
Rec #: 2003
Notes: Cochrane Central database. Using Smart Source Parsing

KQ #3 (race subgroup)
Brewster LM, van Montfrans GA, Kleijnen J. Systematic review: antihypertensive drug therapy in black patients. Ann Intern Med 2004;141:614-27.
Rec #: 2040
Pulled from Content Expert files

KQ #3 (elderly subgroup)
Malacco E, Vari N, Capuano V, et al., for the Val-Syst Investigators. A randomized, double-blind, active-controlled, parallel-group comparison of valsartan and amlodipine in the treatment of isolated systolic hypertension in elderly patients: the Val-Syst study. Clin Ther 2003;25:2765-80.
Rec #: 2045
Notes: Public Comments

Introduction (Clinical Practice Guideline)
National Kidney Foundation. K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. American Journal Kidney Diseases 2004;43(suppl 1):S1-S290.
Rec #: 2041
Pulled from Content Expert files

Appendix D. Bibliography of Excluded Articles

Bakris GL, Siomos M, Richardson D, et al. ACE inhibition or angiotensin receptor blockade. impact on potassium in renal failure. VAL-K Study Group. *Kidney Int* 2000;58:2084-92. [Rec#: 58]
> Notes: Reason for Exclusion: Wrong Outcome.

Bohm M, Sachse A: Safety and tolerability of eprosartan in combination with hydrochlorothiazide. *Drug Safety* 2002;25:599-611. [Rec#: 205]
> Notes: Reason for Exclusion: Wrong Publication Type.

Bremner AD, Baur M, Oddou-Stock P, Bodin F: Valsartan: long-term efficacy and tolerability compared to lisinopril in elderly patients with essential hypertension. *Clinical & Experimental Hypertension* 1997;19:1263-85. [Rec#: 214]
> Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Bremner AD, Mehring GH, Meilenbrock S: Long-term systemic tolerability of valsartan compared with lisinopril in elderly hypertensive patients. *Advances in Therapy* 1997;14:245-253. [Rec#: 215]
> Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Brenner BM eal. The Losartan Renal Protection Study: rationale, study design and baseline characteristics of RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan). *J Renin Angiotensin Aldosterone Syst* 2000;1(4):328-35. [Rec#: 1068]
> Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Cheung R, Lewanczuk RZ, Rodger NW, et al: The effect of valsartan and captopril on lipid parameters in patients with type II diabetes mellitus and nephropathy. *International Journal of Clinical Practice* 1999;53:584-92. [Rec#: 248]
> Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Chrysant SG, Wombolt DG, Feliciano N, Zheng H: Long-term efficacy, safety, and tolerability of valsartan and hydrochlorothiazide in patients with essential hypertension. *Current Therapeutic Research, Clinical & Experimental* 1998;59:762-772. [Rec#: 253]
> Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Dahlof B, Devereux RB, Julius S, et al: Characteristics of 9194 patients with left ventricular hypertrophy: the LIFE study. Losartan Intervention For Endpoint Reduction in Hypertension. *Hypertension* 1998;32:989-97. [Rec#: 280]
> Notes: Reason for Exclusion: Wrong Publication Type.

De Rosa ML, de Cristofaro A, Rossi M, et al: Irbesartan effects on renal function in patients with renal impairment and hypertension: a drug-withdrawal study. *Journal of Cardiovascular Pharmacology* 2001;38:482-9. [Rec#: 292]
> Notes: Reason for Exclusion: Wrong Study Design.

Degl' Innocenti A, Elmfeldt D, Hansson L, et al: Cognitive function and health-related quality of life in elderly patients with hypertension - Baseline data from the Study on COgnition and Prognosis in the Elderly (SCOPE). *Blood Pressure* 2002;11:157-165. [Rec#: 295]
> Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Erdmann E, George M, Voet B, et al: The safety and tolerability of candesartan cilexetil in CHF. *Journal of the Renin-Angiotensin-Aldosterone System* 2000;1:31-6. [Rec#: 338]
> Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Faulhaber HD, Mann JF, Stein G, et al: Effect of valsartan on renal function in patients with hypertension and stable renal insufficiency. *Current Therapeutic Research, Clinical & Experimental* 1999;60:170-183. [Rec#: 345]
Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Fernandez-Andrade C, Russo D, Iversen B, et al: Comparison of losartan and amlodipine in renally impaired hypertensive patients. *Kidney International Supplement* 1998;68:S120 [Rec#: 346]
Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Freytag F, Holwerda NJ, Karlberg BE, Meinicke TW, Schumacher H: Long-term exposure to telmisartan as monotherapy or combination therapy: Efficacy and safety. *Blood Pressure* 2002;11:173-181. [Rec#: 373]
Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

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Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Gansevoort RT, de Zeeuw D, de Jong PE: Is the antiproteinuric effect of ACE inhibition mediated by interference in the renin-angiotensin system? *Kidney International* 1994;45:861-7. [Rec#: 387]
Notes: Reason for Exclusion: Wrong Outcome.

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Notes: Reason for Exclusion: Wrong Outcome.

Giles TD, Bakris GL, Smith DHG, Davidai G, Weber MA: Defining the antihypertensive properties of the angiotensin receptor blocker telmisartan by a practice-based clinical trial. *American Journal of Hypertension* 2003;16:460-466. [Rec#: 394]
Notes: Reason for Exclusion: Wrong Publication Type.

Goldberg AI, Dunlay MC, Sweet CS: Safety and tolerability of losartan compared with atenolol, felodipine and angiotensin converting enzyme inhibitors. *Journal of Hypertension Supplement* 1995;13:S77-S80 [Rec#: 399]
Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Goldberg AI, Dunlay MC, Sweet CS: Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. *American Journal of Cardiology* 1995;75:793-5. [Rec#: 400]
Notes: Reason for Exclusion: Wrong Publication Type.

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Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

Havranek EP, Thomas I, Smith WB, et al: Dose-related beneficial long-term hemodynamic and clinical efficacy of irbesartan in heart failure. *Journal of the American College of Cardiology* 1999;33:1174-81. [Rec#: 441]
Notes: Reason for Exclusion: Wrong Study Design.

Holdaas H, Hartmann A, Berg KJ, Lund K, Fauchald P: Renal effects of losartan and amlodipine
    in hypertensive patients with non-diabetic nephropathy. *Nephrology Dialysis
    Transplantation* 1998;13:3096-102. [Rec#: 449]
        Notes: Reason for Exclusion: Wrong Outcome.

Ilson BE, Martin DE, Boike SC, Jorkasky DK: The effects of eprosartan, an angiotensin II AT1
    receptor antagonist, on uric acid excretion in patients with mild to moderate essential
    hypertension. *Journal of Clinical Pharmacology* 1998;38:437-41. [Rec#: 471]
        Notes: Reason for Exclusion: Wrong Outcome.

Jacobsen P, Andersen S, Rossing K, Hansen BV, Parving HH: Dual blockade of the renin-
    angiotensin system in type 1 patients with diabetic nephropathy. *Nephrology Dialysis
    Transplantation* 2002;17:1019-24. [Rec#: 475]
        Notes: Reason for Exclusion: Wrong Outcome.

Julius S, Kjeldsen SE, Brunner H, et al: VALUE trial: Long-term blood pressure trends in 13,449
    patients with hypertension and high cardiovascular risk. *American Journal of
    Hypertension* 2003;16:544-548. [Rec#: 485]
        Notes: Reason for Exclusion: Wrong Outcome.

Kavgaci H, Sahin A, Onder Ersoz H, Erem C, Ozdemir F: The effects of losartan and fosinopril
    in hypertensive type 2 diabetic patients. *Diabetes Research & Clinical Practice*
    2002;58:19-25. [Rec#: 495]
        Notes: Reason for Exclusion: Wrong Outcome.

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    of type 2 diabetes and nephropathy: lessons from the RENAAL study. *American Journal
    of Kidney Diseases* 2003;41:S22-5. [Rec#: 499]
        Notes: Reason for Exclusion: Wrong Publication Type.

Kincaid-Smith P, Fairley K, Packham D: Randomized controlled crossover study of the effect on
    proteinuria and blood pressure of adding an angiotensin II receptor antagonist to an
    angiotensin converting enzyme inhibitor in normotensive patients with chronic renal
    disease and proteinuria. *Nephrology Dialysis Transplantation* 2002;17:597-601. [Rec#:
    504]
        Notes: Reason for Exclusion: Wrong Outcome.

Kloner RA, Weinberger M, Pool JL, et al: Comparative effects of candesartan cilexetil and
    amlodipine in patients with mild systemic hypertension. Comparison of Candesartan and
    Amlodipine for Safety, Tolerability and Efficacy (CASTLE) Study Investigators.
    American Journal of Cardiology 2001;87:727-31.
     Rec#: 513]
        Notes: Reason for Exclusion: Wrong Outcome.

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    with chronic glomerulonephritis. *Journal of the Renin Angiotensin Aldosterone System*
    2002;3:167-75. [Rec#: 529]
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Notes: Reason for Exclusion: Unable to Retrieve Given Available Resources.

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    Notes: Reason for Exclusion: Wrong Publication Type.

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    Notes: Reason for Exclusion: Wrong Publication Type.

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