Drug Class Review
on
Angiotensin II Receptor Antagonists

Final Report

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

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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 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, alone or in combination with an ACEI, angiotensin II receptor antagonist, beta-adrenergic blocker, or calcium channel blocker in patients with HTN. 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** (2001) [3]	HF	An angiotensin II receptor antagonist is recommended in patients with HF who are unable to tolerate an ACE inhibitor due to angioedema or cough
ADA*** (2003) [4]	DM and renal disease	An angiotensin II receptor antagonist should be strongly considered in the treatment of patients with HTN and type 2 DM and macroalbuminuria, nephropathy, or renal insufficiency, and an ACEI or angiotensin II receptor antagonist may be considered in the management of HTN in patients with type 2 DM and microalbuminuria

* 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 Evaluation and Management of Chronic Heart Failure in the Adult
*** Position statement of the American Diabetes Association

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.[5-11] 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**	DM Nephropathy***
Candesartan	X			
Eprosartan	X			
Irbesartan	X			X
Losartan	X	X		X
Olmesartan	X			
Telmisartan	X			
Valsartan	X		X	

* Reduction in the risk of stroke in patients with HTN and LVH (the manufacturer's product information also states that there is evidence that this benefit does not apply to black patients)
** Treatment of HF [New York Heart Association (NYHA) class II-IV] in patients who are unable to tolerate an ACEI
*** Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (> 300mg/day for irbesartan; urinary albumin to creatinine ratio ≥ 300mg/g for losartan) in patients with type 2 DM and HTN

As the angiotensin II receptor antagonists are all effective in lowering blood pressure (BP) and are approved for the management of patients with HTN,[12] 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 (≥ 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.[13] 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.[14]

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[15] 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.

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.

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?

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. 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. Interpretation of active-controlled trials was limited by the use of different scales for measuring quality of life and the use of different comparator agents.

Head-to-head trials

We identified no relevant head-to-head trials.

Active-controlled trials

We identified no active-controlled trials that evaluated the effect of an angiotensin II receptor antagonist on all-cause mortality, CV mortality, or CV events (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.[16]

We identified five active-controlled trials (two with placebo control) of fair quality that specifically evaluated the quality of life in patients with HTN being treated with losartan,[17,18] candesartan,[19] or eprosartan.[20,21]

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 two trials, the exclusion criteria were not reported, and only two used intent-to-treat analyses. 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),[22] 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.

Nine active-controlled trials were excluded due to the wrong outcome [23-30] and wrong publication type.[31]

End-stage renal disease or deterioration of renal function

One, long-term, randomized, double-blind, controlled trial[16] 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 [17]	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[18]	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*[19]	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*[20]	132	6 weeks	PGWB index	No significant differences between treatments in their effects on QOL	Placebo= Eprosartan < Enalapril (NS after adjustment)
Eprosartan vs. Enalapril[21]	523	26 weeks	PGWB index	No significant differences between treatments at monotherapy endpoint (without HCTZ) 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	Eprosartan < Enalapril (P=0.001) at monotherapy endpoint
Losartan vs. Enalapril [32]	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.[18,20,21] In the trial with losartan,[18] 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,[20] 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,[21] 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

Two multicenter, placebo-controlled trials of fair quality were included in the analysis.[33,34] These trials were rated fair due to post-randomization exclusions and the original placebo-controlled design included the addition of open-label antihypertensive therapy,[33] and inadequate description of method for randomization and allocation concealment.[34] Details of these trials are included in Evidence Table 2 and Quality Table 2. Seven placebo-controlled trials were excluded for the following reasons: wrong outcome;[35-39] wrong publication type;[40] wrong design.[41]

The Study on Cognition and Prognosis in the Elderly (SCOPE),[33] 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[34] 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.

All-cause mortality

All-cause mortality, a secondary endpoint of SCOPE,[33] was not significantly different in the candesartan group compared to active control.

Cardiovascular mortality

In SCOPE,[33] 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[33] 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).

End-stage renal disease or deterioration of renal function

Renal function was not a pre-specified endpoint in the SCOPE trial. In IRMA-2,[34] 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.

Quality of life

The SCOPE[42] and IRMA-2[34] trials did not report results on quality of life.

Systematic reviews

We identified one good quality systematic review[43] 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.

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. The only available randomized controlled trial was one comparing losartan with atenolol in patients with HTN and LVH that reported superiority of losartan for the outcomes of the primary composite endpoint of CV morbidity and mortality (primarily due to the reduction in stroke). 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 one active-controlled trial, the LIFE study[44] that compared the effect of losartan to the beta-adrenergic blocker atenolol in reducing CV morbidity and mortality in patients with HTN and LVH. Three substudies were also conducted in the patients enrolled in the LIFE study that evaluated patients without vascular disease,[45] patients with isolated systolic hypertension (ISH),[22] and patients with DM.[46] These trials are described in detail in Evidence Table 3 and Quality Table 3. One active-controlled trial was excluded due to wrong outcome (reported results of BP reduction, cardiac morbidity and mortality results pending).[47]

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 AIIRAs, beta-adrenergic blockers, or ACEIs) to achieve target BP goal < 140/90 mm Hg. The trial was of good quality.[18,44]

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,[44] 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.[45] Losartan statistically significantly reduced all-cause mortality compared to atenolol in both the pre-specified substudies with ISH[22] and patients with DM.[46]

Cardiovascular mortality

In the LIFE study,[44] 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),[45] patients with ISH (P=0.06),[22] and patients with DM (P=0.031).[46]

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).[22] 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.[22]

In the LIFE trial,[44] there were 533 black patients included (6% of the patient population). In a subgroup analysis of these patients (unpublished data),[48] 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. 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.[8]

In the substudies of patients without vascular disease[45] and those with ISH,[22] 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)[45] and in patients with ISH (P=0.02).

Patients in the DM substudy[46] 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.

Quality of life

Quality of life was not assessed in the LIFE study.[44]

Placebo-controlled trials

We identified no relevant placebo-controlled trials.

Systematic reviews

We identified no relevant systematic reviews.

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.[49] 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.[50] 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, 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).[49,50] The Valsartan in Acute Myocardial Infarction Trial (VALIANT)[49] 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)[50] 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[49-52] or evidence of left ventricular systolic dysfunction based on ejection fraction.[49] 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,[49] 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,[50] 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.[49,50]

Cardiovascular mortality

Cardiovascular mortality, a secondary endpoint in VALIANT[49] and a pre-specified endpoint in OPTIMAAL,[50] 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.[49]

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.[50] 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[49] and OPTIMAAL[50] were not reported in the results of these two publications.

Placebo-controlled trials

We identified no relevant placebo-controlled trials.

Systematic reviews

We identified no relevant systematic reviews.

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 CV death and HF hospitalizations in patients where it was added to standard therapy[53] and in patients intolerant to an ACEI,[54] but not in patients with a LVEF > 40%.[55] All-cause mortality was not significantly reduced in these trials. In a pre-specified analysis of patients with LVEF $\leq$ 40%, there was a significant reduction in all-cause mortality. In one good quality placebo-controlled trial,[56] valsartan reduced the combined 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,[57] 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.[54,58] 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.[56] 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. It is difficult to compare the results of these trials as the endpoints varied and there were slight differences in patient populations studied.

Three placebo-controlled trials and six active-controlled trials, all of fair quality, evaluated symptom improvement in patients with HF. Symptoms of HF were improved with candesartan[59] and losartan[60,61] compared to placebo, and were similar with candesartan,[61] losartan,[62-64] telmisartan,[65] and valsartan[66] compared to an ACEI, although different ACEI comparators were used.

Three placebo-controlled trials and 3 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[61] and valsartan[58] compared to placebo and were also similar to treatment with an ACEI.[66,67] Quality of life was reported to be unchanged with candesartan.[68] Not enough data were available to assess the results with telmisartan compared to an ACEI.[65] No data were available for eprosartan or olmesartan, and limited data were available for irbesartan. Due to the use of a modified MLHF instrument in one trial,[61] 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

Nine active-controlled trials that evaluated the effect of candesartan, losartan, telmisartan, or valsartan in patients with HF were included. One was of good quality[57] and eight were fair quality (due to inadequate description of randomization and/or allocation concealment, 3 did not report patients who were lost to follow-up, 2 did not use an intent-to-treat analysis, complete data were not available in one trial, and one trial was a pilot study).[62-67,69] 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).[69] 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,[57] 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). 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.[70] 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[71,72] 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

Six 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 two used an intent-to-treat analyses) assessed symptomatic improvement.[55,57-60] Three evaluated losartan,[62-64] one telmisartan,[65] and one valsartan.[66] A pilot study evaluating candesartan is reported above.[71] 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). 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.[65-67] One study compared losartan with captopril,[67] another valsartan with enalapril,[66] and the other telmisartan with enalapril.[65] All three 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.[67]

Placebo-controlled trials

Eleven 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. Five were of good quality,[53-56,73] five were fair quality (inadequate description of randomization and/or concealment, two did not use an intent-to-treat analysis, significant difference in baseline groups in one study, large number of post-randomization exclusions in another)[58-61,68] 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).[74] Two trials were excluded due to wrong outcome (LVEF and central hemodynamic and neurohormonal effects)[75] and wrong design (dose-finding study).[76]

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[73] incorporated results of three separate randomized, multicenter, double-blind trials evaluating the effect of candesartan 4mg once daily, titrated to 32mg once daily added 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.[53-55]

The primary outcome for CHARM-Overall[73] 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). In a pre-specified 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).[73]

The CHARM-Alternative trial[54] 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[55] 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[53] randomized 2548 patients with LVEF $\leq$ 40% to candesartan 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 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 conflicts with the results of Val-HeFT in this subgroup of patients (discussed in further detail below).

The Valsartan Heart Failure Treatment (Val-HeFT) study[56] 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. 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 366 patients on valsartan but 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).

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)***	0.08	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[56] and CHARM-Added[53] trials, the subgroup of patients receiving an angiotensin II receptor antagonist in combination with an ACEI and beta-adrenergic blocker were analyzed. Based on the results of the subanalysis of Val-HeFT[56] that 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 recommends that valsartan be considered in patients with HF who are unable to tolerate treatment with an ACEI.[11] The CHARM-Added trial[53] 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.

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.

In the CHARM-Alternative trial[54] 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,[58] 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.

Symptomatic improvement

Three trials were designed to evaluate symptomatic improvement,[59-61] in addition to Val-HeFT discussed above.[56] Dose-related improvements in total exercise time (by bicycle ergometry) and the dyspnea-fatigue index was seen with candesartan. Improvements in NYHA functional class were seen more frequently with candesartan compared to placebo, although the differences were not statistically significant.[59] In a study with losartan,[60] 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,[61] 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.[56]

Quality of life

The subgroup analysis of patients in Val-HeFT who were not receiving an ACEI,[58] 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. 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,[61] that was statistically significant compared to placebo (P<0.05). In the 12 week pilot Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE)[68] of 270 patients, quality of life was unchanged with candesartan (as assessed by the MLHF questionnaire), but declined 9.5% with placebo.

Systematic reviews

One meta-analyses in patients with HF,[77] 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 (meta-analysis was conducted prior to the publication of CHARM). Another meta-analysis of patients with HF (published in 2000)[78] 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.

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.[79] Another active-controlled trial reported the change in CrCl did not differ significantly with the combination of candesartan plus lisinopril compared to either monotherapy.[80] In one small trial of patients with non-diabetic nephropathy,[81] 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.[82] 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 two active-controlled trials in patients with diabetic nephropathy (one evaluating albumin excretion rate and GFR with valsartan vs. captopril vs. placebo[83] and the other evaluating albuminuria with losartan and enalapril compared to placebo[84]) 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.[85,86]

The outcome measures used in these two trials 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. 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

Six 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[79], four were fair quality (due to inadequate description of method randomization and/or concealment, two were open-label, and one did not include an intent-to-treat analysis),[80,82-84]and one was poor quality[87] (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;[79] candesartan vs. lisinopril vs. candesartan plus lisinopril;[80] valsartan vs. benazepril vs. valsartan plus benazepril.[82] The other two trials were a comparison of valsartan vs. captopril vs. placebo[83] and losartan vs. enalapril vs. placebo.[84]

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[79] 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[80] 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.[82] 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,[83] there was a statistically significant decrease in albumin excretion rate with valsartan 80mgcompared 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[84] 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.

Quality of life

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

Placebo-controlled trials

Three placebo-controlled trials[81,85,86] 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,[85,86] and one was of fair quality (due to inadequate description of randomization and concealment and small patient population).[81] Two of the trials were in patients with type 2 diabetic nephropathy,[85,86] and one in non-diabetic nephropathy.[81] Three trials were excluded due to wrong outcome[88-90]

The Irbesartan Type 2 Diabetic Nephropathy Trial (IDNT)[85] 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.

In the multicenter, randomized, double-blind Reduction of Endpoints in Patients with NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial,[86] 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.

Nine patients were randomized to valsartan 80mg once daily or placebo in a double-blind trial of 6 months duration[81] evaluating albuminuria and GFR.

End-stage renal disease or deterioration of renal function

In IDNT,[85] the primary endpoint (composite doubling sCr, onset of ESRD, or all-cause mortality) was statistically significantly reduced with irbesartan compared to patients on placebo (RR 0.80 95% CI 0.66-0.97, P=0.02; calculated RRR from events 16.3%, calculated RR 0.84 95% CI 0.72-0.98, ARR 6.4%, calculated NNT=16 95% CI 8-119 based on crude rates of events). 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. In RENAAL,[86] 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.

A comparison of these results 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,[81] 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[43] was identified that evaluated the effect of the angiotensin II receptor antagonists as antihypertensive therapy in patients with DM (previously discussed under Key Question 1a. in patients with HTN). Two of the trials discussed above were included in the systematic review and meta-analyses.[85,86] 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 0.54-0.89).

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 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, and valsartan for patients with nephropathy. Refer to Table 9 on adverse events in randomized controlled trials. No data were available for olmesartan.

Reported adverse effects of interest included hypotension (2-13.3%; 15.1% requiring dose reduction in one study[49]), dizziness (4.3-10%), and angioedema (0.1%-0.4%).

Hyperkalemia was reported in 4.5% of patients in one trial,[79] requiring dose reduction in 1.3% of patients in another trial,[49]and requiring discontinuation in 0.6-1.9% of patients.[69,85] Dose reduction due to renal causes was reported in 4.9% of patients in one trial.[49] Cough was reported in 2-9.3% of patients, with 12.8-16% in patients with a history of ACEI induced cough.[19,20] 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,[19] and 12.8% of patients on eprosartan, 28.2% on enalapril, and 7.3% of patients on placebo.[20]

For the placebo-controlled trials included in this review of good or fair quality, data were available with candesartan and irbesartan for patients with HTN, losartan for patients with high CV risk factors, losartan and valsartan for patients with recent MI, candesartan, 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 (20.9-23.9%; 1.6% requiring discontinuation), and angioedema (0.03-0.16%; up to 4.5% in one study of patients intolerant to an ACEI[68]). 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.[53-56,61,68,73,86] Doubling of sCr was reported in 5.5-6% of patients in two of the CHARM trials.[54,55] In one study, cough was reported in 68.2% of HF patients with a history of ACEI induced cough.[68] Discontinuation due to cough was reported in 0.2% of patients in one study of patients with HF.[54]

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[18,32] in patients with HTN, losartan[22] in patients at high CV risk, losartan[50] and valsartan[49] in patients with recent MI, valsartan[83] in patients with nephropathy, and losartan[57,62-64,67,69] and valsartan[66] in patients with HF). Withdrawal rates due to adverse events were higher than control in only a few trials (candesartan[19] in patients with HTN, and telmisartan[65] 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.

Withdrawal rates due to adverse events were generally less than placebo (candesartan[42] and irbesartan[34] in patients with HTN, losartan[86] in patients with nephropathy) except for patients on candesartan[53-55,59,68,73] and valsartan[60,61] in patients with HF. No data were available for eprosartan, olmesartan, or telmisartan. 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. No data were available for eprosartan or olmesartan. 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.[45]

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.[34] 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.[59]

Two systematic reviews and meta-analyses, one in HF[77] and one including trials that evaluated the use of angiotensin II receptor antagonists as antihypertensive therapy in patients with DM[43] were conducted. In patients with HF,[77] there was not a statistically significant difference in the pooled rate of mortality or HF hospitalizations between treatment with an angiotensin II receptor antagonist compared to the control group. This systematic review included Val-HeFT,[56] ELITE II,[57] and RESOLVD,[71] all three of which reported a slight but insignificant increase in mortality compared to the control group. The results of the CHARM-Overall program[73] were not included in the analysis where candesartan reduced all-cause mortality (borderline significance) in patients with HF. According to the systematic review including IDNT, RENAAL, and the substudy of LIFE in patients with DM, there was not a statistically significant difference in the combined rate of mortality with an angiotensin II receptor antagonist vs. placebo, and a non-significant reduction compared to control therapy.[43]

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.[91-95] 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[92]; 36.7% vs. 87.5%, P<0.001[95]; 29.2% vs. 71.7%[93]). 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).[94] 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.[91] 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.[96] Two of the studies assessed the effect of valsartan on sexual function in comparison to a beta-adrenergic blocker by patient questionnaire.[32,97] 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.[32,97]

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.[53-56,61,68,73,86] Doubling of sCr was reported in 5.5-6% of patients in two of the CHARM trials.[54,55]

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,[54] 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,[54] 3 of 1013 patients randomized to candesartan experienced angioedema. One of these patients 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.[5] Facial edema has been reported in 5 patients receiving eprosartan.[6] Facial edema

has also been reported with irbesartan and very rarely, angioedema, in post-marketing experience.[7] 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.[8] There have been five reports of facial edema with olmesartan.[9] One case of angioedema was reported in a total of 3,781 patients treated with telmisartan.[10] 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.[11]

There were no systematic reviews available comparing the angiotensin II receptor antagonists for specific adverse effects or withdrawals due to specific adverse events.

One retrospective cohort study[98] (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. Angioeneurotic 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. Since all of the 95% confidence intervals overlap (with one exception), we cannot conclude that differences between drugs exist in the rate of adverse events. The one exception was the occurrence of dizziness/vertigo in patients treated with valsartan. However, this pooled result was due to a statistically significant difference in this outcome seen in only one trial[56] 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

			Placebo		Intervention Groups				
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI	Zelen p-values
Hypotension	Candesartan	4	654	6558	784	7092	1.21	(1.07, 1.36)	< 0.0001
Hypotension	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Hypotension	Irbesartan	1	0	52	7	57	NC	NC	NC
Hypotension	Losartan	0	NR	NR	NR	NR	NC	NC	NC
Hypotension	Valsartan	3	30	2709	61	2758	2.06	(1.30, 3.34)	0.0756
Dizziness/Vertigo	Candesartan	1	492	2460	518	2477	1.06	(0.92, 1.22)	NC
Dizziness/Vertigo	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Dizziness/Vertigo	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	Valsartan	3	45	2709	84	2758	2.00	(1.34, 3.02)	0.0012
Increased sCr/Renal impairment	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	Losartan	1	9	762	11	751	1.24	(0.47, 3.42)	NC
Increased sCr/Renal impairment	Valsartan	1	5	2499	28	2511	5.62	(2.14, 18.68)	NC
Cough	Candesartan	2	62	117	132	241	1.20	(0.71, 2.02)	0.2797
Cough	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	Valsartan	1	1	29	4	62	1.92	(0.18, 98.44)	NC
Hyperkalemia	Candesartan	2	25	3887	95	3982	3.62	(2.30, 5.89)	0.0637
Hyperkalemia	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Hyperkalemia	Irbesartan	1	2	569	11	579	5.48	(1.19, 51.14)	NC
Hyperkalemia	Losartan	1	4	762	8	751	2.04	(0.54, 9.30)	NC
Hyperkalemia	Valsartan	0	NR	NR	NR	NR	NC	NC	NC
Bronchitis/flu/upper respiratory infection	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	Valsartan	1	0	29	0	62	NC	NC	NC
Nausea/Vomiting	Candesartan	0	NR	NR	NR	NR	NC	NC	NC
Nausea/Vomiting	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Nausea/Vomiting	Irbesartan	1	11	52	3	57	0.21	(0.04, 0.86)	NC
Nausea/Vomiting	Losartan	1	0	17	1	16	NC	NC	NC
Nausea/Vomiting	Valsartan	1	1	29	1	62	1.02	(0.52, 2.01)	NC
Angioedema	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

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
Headache	Candesartan	0	NR	NR	NR	NR	NC	NC	NC
Headache	Eprosartan	0	NR	NR	NR	NR	NC	NC	NC
Headache	Irbesartan	1	6	52	11	57	1.82	(0.56, 6.54)	NC
Headache	Losartan	0	NR	NR	NR	NR	NC	NC	NC
Headache	Valsartan	1	1	29	1	62	0.46	(0.01, 37.31)	NC
GI disorder/upset	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	Valsartan	1	0	29	1	62	NC	NC	NC

OR: Odds Ratio
CI: Confidence Interval
NR: Not Reported
NC: Not Calculated

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.

Summary

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.[8,22,48,56] 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 11-54% of patients enrolled in the trials were women. It appears that women derive the 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[56] whereas data with candesartan showed no difference in mortality, but a significant decrease in the combined endpoint of CV mortality and HF hospitalizations.[54] From the available information, it can be concluded that the combination of an angiotensin II receptor antagonist with an ACEI and beta-adrenergic blocker does not reduce all-cause mortality in patients with HF (and may increase mortality based on a subgroup analysis). The role of combination therapy in reducing CV events or hospitalization is unclear as the evaluation was by subgroup analysis and with different endpoints and angiotensin II receptor antagonists (e.g., candesartan: combined CV mortality and HF hospitalizations; valsartan: combined all-cause death, HF hospitalizations, cardiac arrest with resuscitation, IV therapy). There are inadequate data to determine whether there is a difference between the angiotensin II receptor antagonists.

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.

Three 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[55,56,73] or HTN.[17] Randomized controlled trials conducted with an angiotensin II receptor antagonist in older patients with hypertension showed that treatment with candesartan,[99,100] eprosartan,[101] irbesartan,[87] or valsartan [102] was effective in lowering blood pressure and well tolerated in this patient population.

The average age of patients enrolled in the trials included in the review were 55-76 years for HTN (candesartan, losartan), 67 (70 in a subgroup analysis) for high CV risk (losartan), 65-67 for recent MI (losartan, valsartan), 58-74 for HF (candesartan, irbesartan, losartan, telmisartan, valsartan) and 42-60 for nephropathy (candesartan, irbesartan, losartan, 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.[56] 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,[22] there were 533 black patients included (6% of the patient population). In a subgroup analysis of these patients (unpublished data),[48] the primary endpoint (CV death, nonfatal stroke, nonfatal MI) occurred in 29 of 263 patients (11%) on atenolol compared to 46 of 270 patients (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.[8]

As with the ACEIs, the angiotensin II receptor antagonists are considered not to be 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.[2,103-105]

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.[106]

The incidence of angioedema in patients taking ACEIs is approximately 0.1-1.2%.[107] 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.[108] 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 [86] including 18% Hispanic and 16% Asian patients, and another enrolling over 200 patients, 100% who were Japanese.[79]

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.[109]

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[46] and in patients with HF[55-57,73].

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% of patients at high CV risk;[22] 63%[19] and 54%[42] of patients with HTN; 53% of patients with nephropathy;[79] 51%[60] and 80%[61] of patients with HF. In the active-controlled and placebo-controlled trials, women were included as 46-54% of patients in the HTN trials, as 54% of patients at high CV risk, as approximately 30% of patients in the recent MI trials, as 11-51% 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,[22] evaluated subgroups of patients based on their comorbidities. The primary composite endpoint of CV morbidity and mortality was decreased in the patients receiving losartan in the subgroup of patients without vascular disease,[45] patients with DM,[46] and patients with ISH.[22]

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.[110]

Two trials with losartan,[111,112] one which was a head-to-head crossover comparison with irbesartan,[112] evaluated the effect of an angiotensin II receptor antagonist on serum uric acid in patients with asymptomatic[111] or symptomatic[112] hyperuricemia. Treatment with losartan resulted in a significant reduction in serum uric acid compared to placebo in hypertensive patients with thiazide-induced hyperuricemia.[111] 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.[112]

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.

Two 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, as well as patients treated with an angiotensin II receptor antagonist who were not on an ACEI.[54,56] Based on these results, treatment with candesartan showed a beneficial effect in reducing CV death and HF hospitalizations[54] and valsartan in reducing combined morbidity and mortality[56] in patients with HF who are unable to tolerate an ACEI. 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[56] whereas another trial with candesartan[54] 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.[79]

In vitro studies have demonstrated inhibition of the formation of irbesartan metabolites by cytochrome 2C9 substrates or inhibitors[7] 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.[7] 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.[10] In a subgroup analysis of digoxin levels in patients participating in the REPLACE trial,[113] 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.[10] 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: QOL)	No head-to-head trials comparing AIIRAs in HTN. **Candesartan** (one active-controlled trial) 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. Candesartan (one active-controlled trial) improved one parameter of QOL compared to placebo in patients with ACEI-induced cough. **Eprosartan** (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. 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	Fair (losartan)	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 (three 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.
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 superior or non-inferior to captopril in reducing all-cause mortality in a similar patient population. **Valsartan** (one active-controlled trial) is as effective as 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, 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 one combining results of these trials) reduced CV death and HF hospitalizations (including patients on an ACEI and beta-blocker and those who were ACEI intolerant). There was no significant effect on mortality. Also improved symptoms of HF (two placebo-controlled trials, one active-controlled trial). **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 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). **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) 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. **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. **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 (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; 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. 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 triple combination. There are inadequate data to determine whether there is a difference between the AIIRAs.

Table 9. Summary of the Evidence by Drug and Indication

	HTN	High CV Risk	Recent MI	HF	Nephropathy
Candesartan	Reduced non-fatal stroke; some improvement in QOL	NA	NA	Reduced CV death, HF hospitalization (in patients on ACEI and beta-blocker and those ACEI intolerant); no significant effect on mortality; improved HF symptoms	Decrease in CrCl not significant vs. ACEI or combination
Eprosartan	No improvement in QOL	NA	NA	NA	NA
Irbesartan	Reduced onset diabetic nephropathy (300mg)	NA	NA	NA	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	NA
Valsartan	NA	NA	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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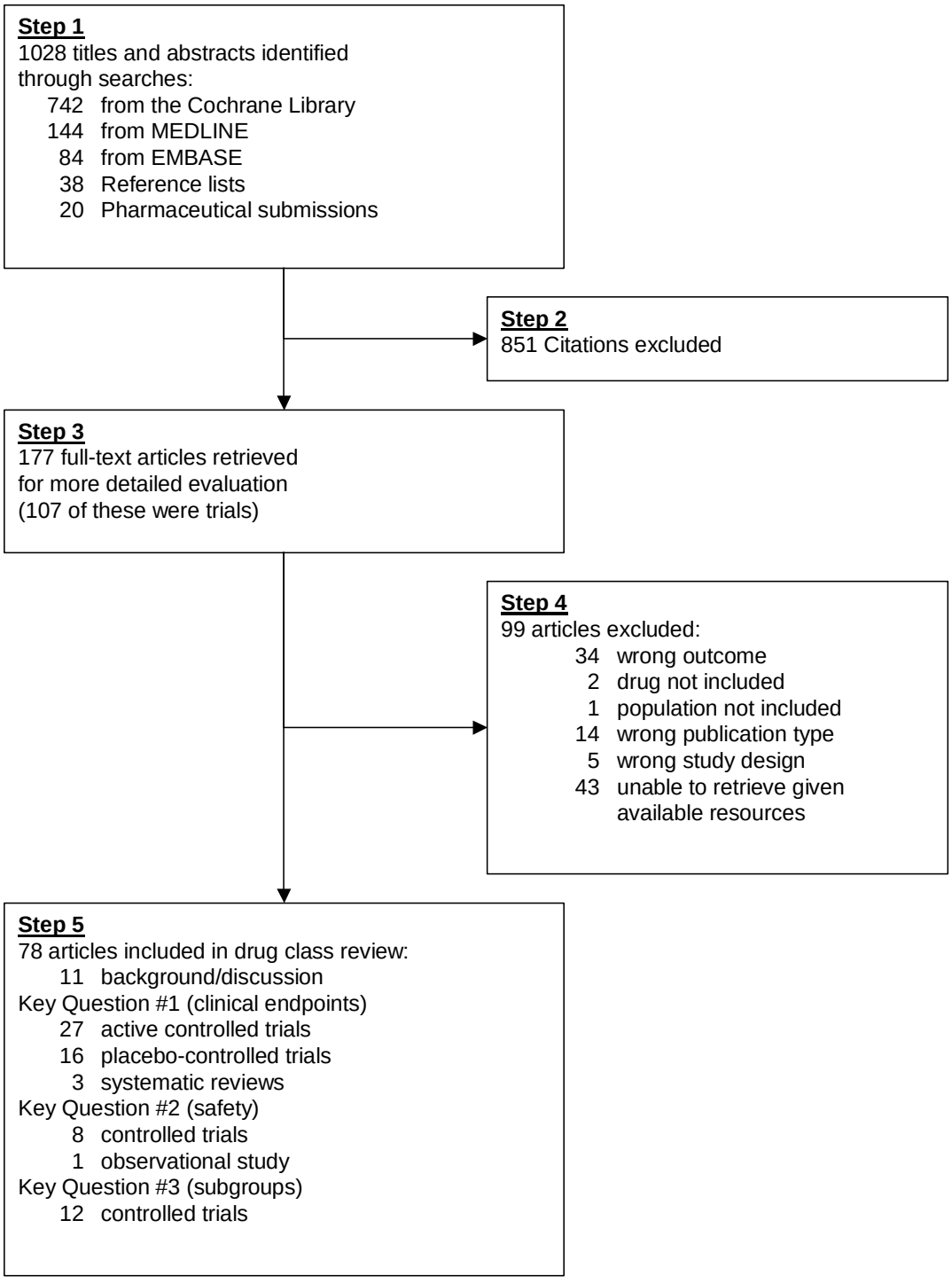
Figure 1 Results of Literature Search



Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions
Tedesco, 1999 Country not stated (Fair)	RCT	Age 30 to 73 with uncomplicated mild to moderate HTN (DBP 90-114 mm Hg on nonpharmacologic therapy)	Losartan 50mg once daily or HCTZ 25mg once daily Mean follow-up 2.2 years
Dahlof, 1997 Sweden, Australia, Finland LOA Study (Fair)	RCT, multicenter	Mild to moderate HTN (DBP 90-115 mm Hg)	Losartan 50mg once daily (if DBP > 90 mm Hg, increased to 100mg); losartan 50mg (if DBP > 90 mm Hg, add HCTZ 12.5mg); amlodipine 5mg once daily (if DBP > 90 mm Hg, increased to 10mg); adjustment occurred at 6 weeks Follow-up 12 weeks

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Tedesco, 1999 Country not stated (Fair)	Two weeks double-blind nonpharmacologic therapy	Not specified
Dahlof, 1997 Sweden, Australia, Finland LOA Study (Fair)	1 week wash-out/4 week placebo run-in	Not specified

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Tedesco, 1999 Country not stated (Fair)	Objective to examine long-term changes in QOL [assessed by 46 item questionnaire appropriate for HTN including symptomatic physical well-being, psychologic well-being, activity, perception of effects of treatment on lifestyle, including social participation, performance, and satisfaction at work; scored disability as a Health Index on a continuum from 0 (death) to 1 (perfect health), and cognitive function [by Sandoz Clinical Assessment Geriatric (SCAG) and Mini-Mental State Examination (MMSE)], and to compare the antihypertensive effect of losartan vs. HCTZ; patients stratified by age (< 60years vs. ≥ 60years). Patients assessed at baseline and 26 months	Mean age 55 (losartan 23 patients < 60 years, 19 ≥ 60 years vs. HCTZ 13 patients < 60 years, 14 ≥ 60 years) 52% male, ethnicity not specified
Dahlof, 1997 Sweden, Australia, Finland LOA Study (Fair)	Objective to compare effect on QOL [assessed by the psychological general well-being (PGWB) index, 22 item questionnaire (22-132 points) with 6 domains (anxiety, depressed mood, positive well-being, self-control, general health, vitality)], BP and drug tolerability. Patients completed a questionnaire at home on the day before visits during weeks -4, 0, 6, and 12 (given to investigator in sealed envelope)	Mean age 58 53% male, 99% white

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Tedesco, 1999 Country not stated (Fair)	Duration of HTN 5 years (significantly longer in patients ≥ 60 years, P<0.001 losartan, P<0.01 HCTZ), education 9 years	Number screened not reported/number eligible not reported/69 enrolled	None withdrawn/none lost to fu/69 analyzed
Dahlof, 1997 Sweden, Australia, Finland LOA Study (Fair)	16-23% CVD, 6-7% DM, 39-41% musculoskeletal diseases, 25-26% neurologic and psychiatric disorders, 20-22% respiratory diseases	Number screened not reported/number eligible not reported/898 enrolled	75 did not complete the study/number lost to fu not reported/787 analyzed for QOL

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Results	Results	Method of adverse effects assessment?
Tedesco, 1999 Country not stated (Fair)	QOL main objective: mean (sd) losartan baseline 0.90(0.08) vs. 26 months 0.96 (0.06) (P<0.01; 95% CI -0.08 to -0.02), < 60 years (P<0.003), ≥ 60 years (P<0.02); HCTZ baseline 0.89(0.07) vs. 26 months 0.94(0.08) (P<0.02; 95% CI -0.09 to -0.01), < 60 years (NS), > 60 years (P<0.05)	Reported that ANOVA for BP, MMSE, SCAG, QOL showed a significant difference losartan vs. HCTZ (P<0.001)	Not reported
Dahlof, 1997 Sweden, Australia, Finland LOA Study (Fair)	QOL main objective: total score (after 12 wks) losartan 110.0 vs. 107.5 baseline (P<0.001), losartan + HCTZ 109.8 vs. 108.1 baseline (P=0.002), amlodipine 108.7 vs. 108.2 baseline; improvement in PGWB score in 60% losartan monotherapy, 54% losartan + HCTZ, 50% amlodipine (losartan vs. amlodipine P=0.011) NNT=9 (95% CI 5-30) for losartan monotherapy vs amlodipine	QOL main objective (continued): losartan monotherapy significantly improved anxiety, depressed mood, positive well-being, vitality; losartan + HCTZ significantly improved anxiety, general health, vitality; none of the 6 domains were significantly improved with amlodipine	Monitored at each visit by asking one general (Y/N) question and 24 (Y/N) on specific symptoms; spontaneous reporting

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Tedesco, 1999 Country not stated (Fair)	No complaints of cough or complications in sexual performance; no adverse laboratory events reported	Reported that all patients completed the study	Differences in SCAG, MMSE, 24hr SBP and 24hr DBP all statistically significantly improved at the end of the trial vs. baseline for patients on losartan as well as those in each age subgroup (significant improvement for HCTZ in 24hr SBP and 24hr DBP, and in patients < 60 years). 80% of patients on losartan and 50% patients on HCTZ were satisfied with their therapy and chose to continue
Dahlof, 1997 Sweden, Australia, Finland LOA Study (Fair)	Any discomfort: 22.5% losartan monotherapy, 23.5% losartan + HCTZ, 33.1% amlodipine (P=0.002 amlodipine vs. baseline); dizziness upon standing: 10.1% losartan monotherapy (P=0.028 vs. baseline), 17.1% losartan + HCTZ (P=0.001 vs. baseline), 33.1% amlodipine (P=0.002 amlodipine vs. baseline); no difference in global symptom score (0-24) between groups	94% on losartan monotherapy, 92% on losartan + HCTZ, 89% on amlodipine did not complete the study; 2% on losartan monotherapy, 5% on losartan + HCTZ, 8% on amlodipine withdrew due to adverse experiences (P=0.01 amlodipine vs. losartan monotherapy)	All treatment groups significantly reduced SBP and DBP vs. baseline (P<0.001)

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions
Tanser, 1998 Australia, Canada, Europe, Mexico (Fair)	Multicenter	Male and female outpatients aged 20 to 80 years with primary hypertension and a history of ACE-inhibitor-induced cough	Candesartan 8 mg once daily Enalapril 10 mg once daily Placebo 8 weeks or when patient reported dry cough

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Tanser, 1998 Australia, Canada, Europe, Mexico (Fair)	1-4 week enalapril challenge period Those who experienced dry cough continued to a 1-4 week placebo dechallenge period in which cough had to resolve and be absent on two consecutive visits	HCTZ (12.5 mg) if diastolic BP > 105 mm Hg

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Tanser, 1998 Australia, Canada, Europe, Mexico (Fair)	Symptom Assessment (SA) questionnaire of symptoms using 5-point Likert scale (not at all, a little, moderation, quite a bit, and extremely) Cough frequency rated using 100 mm visual analog scale (1=none of the time to 100=all of the time) Quality of life: 15 of original 24 items in the Minor Symptom Evaluation (MSE) profile for contentment, vitality and sleep; MSE uses 100-mm visual analog scale with lower end of the scale indicating positive feelings and the higher end of the scale negative feelings	60 37% male 81.2% white

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Tanser, 1998 Australia, Canada, Europe, Mexico (Fair)	BMI 29 kg m2 DBP 93 mm Hg SBP 153 mm Hg	Number screened not reported/301 eligible/156 enrolled	Number withdrawn not reported/number lost to fu not reported/154 analyzed

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Results	Results	Method of adverse effects assessment?
Tanser, 1998 Australia, Canada, Europe, Mexico (Fair)	Patients with cough (%) after 8 weeks Placebo=26.9% Candesartan=35.5% (P>0.20 vs placebo) Enalapril=68.2% (P<0.001 vs candesartan) NNT=3 (95% CI 2-6) for candesartan vs enalapril MSE profile contentment: mean difference between candesartan & placebo=7.6mm, 95% CI 0.7 to 14.4mm P=0.03 sleep and vitality: nonsignificant trends	Recorded, either from spontaneous reports by the patient, or in response to an open, nonspecific questions (such as "Have you had any health problems since we last met?"), or as observed by study personnel	

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Tanser, 1998 Australia, Canada, Europe, Mexico (Fair)	Cough Enalapril=31% Candesartan=16% Placebo=11%	Withdrawals due to adverse events Placebo=3/26(11.5%) Candesartan=5/62(8.1%) Enalapril=3/66(4.5%)	Unable to determine percent of patients with HCTZ added in each group

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions
Rake, 2001 U.S. (Fair)	Multicenter	Male and female patients, of at least 18 years of age, with mild to moderate hypertension and a history of ACE inhibitor induced cough; no dry cough and average sitting diastolic BP of 95-114 mm Hg at the last 2 weekly visits of the 4-5 week single-blind, placebo run-in period; development of persistent non-productive dry cough during 3-4 week single-blind period of treatment with enalapril 20 mg daily; no cough at the end of the 2-4 week placebo washout period	Eprosartan 600 mg twice daily Enalapril 20 mg once daily Placebo

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Rake, 2001 U.S. (Fair)	4-5 week single blind placebo run-in 3-4 week single blind treatment with enalapril 20 mg 2-4 week placebo wash-out period	Not reported

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Rake, 2001 U.S. (Fair)	Quality of life: Psychological General Wellbeing Index (PGWB) (anxiety, depressed mood, positive well-being, self-control, general health and vitality; higher scores reflect more positive well-being); sleep disturbance scale; life satisfaction; satisfaction with spouse Pulmonary Questionnaire: self-reported dry unproductive cough Completed at the beginning of the placebo run-in period, during the placebo washout phase just prior to randomization, and at the last visit of the double-blind treatment	56.6 52.3% male Ethnicity not reported

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Rake, 2001 U.S. (Fair)	Diastolic BP=100.7 mm Hg Smoking history=9.1% Smoker's cough=0.7%	231 screened/number eligible not reported/136 enrolled	4(2.9%) withdrawn/0 lost to fu/132 analyzed

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Results	Results	Method of adverse effects assessment?
Rake, 2001 U.S. (Fair)	Quality of life (mean change) *Anxiety* Placebo=(-0.49) Enalapril=0.33 Eprosartan=(-0.14) *Depression* Placebo=(-0.39) Enalapril=0.02 Eprosartan=(-0.18) *Positive well-being* Placebo=0.10 Enalapril=0.40 Eprosartan=0.12 Life satisfaction/Spouse satisfaction/Sleep disturbance=no treatment effects (data nr)	*Self-control* Placebo=(-0.05) Enalapril=(-0.02) Eprosartan=0.00 *General health* Placebo=0.63 Enalapril=(-0.38) Eprosartan=(-0.13) *Vitality* Placebo=0.36 Enalapril=0.60 Eprosartan=0.14 *PGWB Total* Placebo=0.20 Enalapril=0.94 Eprosartan=(-0.29)	Pulmonary Questionnaire: self-reported dry unproductive cough Investigator completion of pulmonary questionnaire

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Rake, 2001 U.S. (Fair)	Self-assessed cough *Definite dry cough* Placebo=2/41(4.9%) Enalapril=5/39(12.8%) Eprosartan=1/39(2.6%) *Probably dry cough* Placebo=0 Enalapril=4/39(10.2%) Eprosartan=1/39(2.6%) *Possible dry cough* Placebo=0 Enalapril=0 Eprosartan=0 *All coughs* Placebo=2/41(4.9%) Enalapril=9/39(23.1%)(p=0.047 for eprosartan vs enalapril) Eprosartan=2/39(5.1%) Investigator reported cough Placebo=3/41(7.3%) Enalapril=11/39(28.2%)NS Eprosartan=5/39(12.8%)	Not reported	

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions
Breeze, 2001 North America, Europe, South Africa (Fair)	Multicenter	Patients aged 18 or more with sustained mild-moderate hypertension (mean sitting diastolic BP between 95 mm Hg and 114 mm Hg inclusive at 3 successive visits	Eprosartan 400-600 mg twice daily Enalapril 5-20 mg once daily Duration 26 weeks

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Breeze, 2001 North America, Europe, South Africa (Fair)	3-5 week placebo run-in period	HCTZ 12.5-25 mg (after 12 weeks if necessary - goal not reported)

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Breeze, 2001 North America, Europe, South Africa (Fair)	Dry unproductive persistent cough assessed by questionnaire Quality of life assessed by Psychological General Wellbeing Index (PGWB) Clinic visits at week 6, 12 and 26	55.7 56.5% male 87.2% white

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Breeze, 2001 North America, Europe, South Africa (Fair)	Cough Status Definite=1.3% Probably=0.6%	Number screened not reported/number eligible not reported/529 enrolled	82/529(15.5%) withdrawn/number lost to fu not reported/523 analyzed

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Results	Results	Method of adverse effects assessment?
Breeze, 2001 North America, Europe, South Africa (Fair)	PGWB scores (between treatment differences in mean change (95% CI)) *Eprosartan:Enalapril (study endpoint/monotherapy endpoint* Anxiety: -0.82(-1.55, -0.99)/-0.58 (-1.21, 0.05) Depression: -0.27(-0.64, 0.11)/-0.07(-0.40, 0.26) Positive well-being: -0.16(-0.68, 0.35)/0.24(-0.25, 0.72) Self-control: -0.50(-0.89, -0.10)/-0.09(-0.44, 0.27) General health: -0.42(-0.82, -0.02)/-0.00(-0.41, 0.41) Vitality: -0.23(-0.75, 0.30)/-0.21(-0.73, 0.31) Total: -2.48(-4.63, -0.32)/-0.79(-2.72, 1.15) Life satisfaction/sleep disturbance/job satisfaction: no between group differences (data nr)	PGWB regression analysis adjusted for baseline values Eprosartan:Enalapril (95% CI; p-value) Anxiety: -0.60(-1.28, 0.07; NS) Depression: -0.19(-0.52, 0.15; NS) Positive well-being i) baseline score ≤19: -0.42 (-0.97, 0.12; NS) ii) baseline score >19: 0.65 (-0.29, 1.60; NS) Self-control: -0.45(-0.81, -0.08; p=0.016) General health: -0.34(-0.70, 0.14; NS) Vitality i) baseline score ≤20: -0.27(-0.94, 0.39, NS) ii) baseline score >20: 0.16(-0.53, 0.85; NS) Total i) baseline score ≤119: -2.32(-4.54, -0.10; P=0.041) ii) baseline score >119: -0.99(-6.13, 4.14; NS)	Assessed by investigator using a questionnaire

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Breeze, 2001 North America, Europe, South Africa (Fair)	<u>Cough incidence (% patients)</u> *Study endpoint analysis* *Definite* Eprosartan=5/247(2%) Enalapril=12/249(4.8%) *Probable/possible* Eprosartan=3/247(1.2%) Enalapril=7/249(2.8%) *Definite/Probable/possible* Eprosartan=8/247(3.2%) Enalapril=19/249(7.6%) *Monotherapy endpoint analysis* *Definite* Eprosartan=4/245(1.6%) Enalapril=15/247(6.1%) *Probable/possible* Eprosartan=1/245(0.5%) Enalapril=9/247(3.6%) *Definite/Probable/possible* Eprosartan=5/245(2.0%) Enalapril=24/247(9.7%) (p=0.001)	<u>Total withdrawals</u> Eprosartan=35/265(13.2%) Enalapril=47/264(17.8%) <u>Withdrawal due to cough</u> Eprosartan=2/265(0.7%) Enalapril=7/264(2.6%)	Reported that open-label HCTZ added at 12 weeks was almost identical in both groups (data not shown)

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions
T	Single center (outpatient clinic)	Essential HTN, classified as WHO stage II (average supine DBP >90 mm Hg and/or SBP > 140 mm Hg)	Enalapril 5-20 mg once daily Losartan 12.5-50 mg once daily Titration generally occurred at 7-day intervals as tolerated if DBP was ≥ 90 mm Hg Duration 3 years

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
T	2-week placebo run-in	Not reported

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
T	Clinic visits after 1, 2, 3, and 4 weeks and every 12 weeks of the 3 year therapy QOL: symptom bother (not at all, little, moderately, quite a bit or extremely), overall health perceptions, psychologic well being, social functioning, sleep disturbance, cognitive functioning and sexual functions	54.9 50% male Ethnicity not reported

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
T	BMI 27.4 kg/m2 SBP 156.9 mm Hg DBP 102.5 mm Hg GFR 97.1 ml/min	Number screened not reported/number eligible not reported/50 enrolled	8(16%) withdrawn/2(4%) lost to fu/42 analyzed

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Results	Results	Method of adverse effects assessment?
T	GFR change (%) Losartan 12.5% increase (P<0.005 vs. baseline) Enalapril 5.3% increase (P=0.085 vs. baseline) Change in GFR: mean(sd) after 3 years of treatment in ml/min Losartan: baseline=96.5 (32.3) follow-up=108.6 (31.12) P<0.005 Enalapril: baseline=94.8 (31.1) follow-up=99.8 (19.6) P=0.085 Quality of life (12 weeks) Losartan=Enalapril on all domains except > bother due to cough with enalapril (12%) vs. lisinopril (2%) (P=0.01) (other data not reported)		Not reported

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
T	Incidence of bother due to cough: Losartan 2% Enalapril 12% (P=0.01)	Total withdrawals Losartan 4/26(15.4%) Enalapril 4/24(16.7%) NS Withdrawal due to adverse events Losartan 0 Enalapril 3/24(12.5%) NS	

Evidence Table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Lithell, 2003 U.S., Canada, Europe SCOPE trial (Fair)	RCT, multicenter	Age 70 to 89 with HTN (treated or untreated 160-179/90-99 mm Hg), MMSE $\geq$ 24	Candesartan 8mg, titrated to 16mg if BP > 160/85 mm Hg or SBP < 10 mm Hg vs. randomization) vs. placebo. If BP > 160/100 mm Hg despite 16mg candesartan (or placebo) addition of open-label antihypertensive treatment was recommended (HCTZ 12.5mg or increase if patient on from baseline), then adding other antihypertensive agents besides an AIIRA or ACEI) Mean follow-up 3.7 years	Open run-in (1 to 3 months) untreated or HCTZ 12.5mg BP 160-179/90-99 mm Hg

Evidence Table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author Year Country Trial Name	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics
Lithell, 2003 U.S., Canada, Europe SCOPE trial (Fair)	Open-label HCTZ 12.5mg (as described under Interventions) or increase, with addition of other antihypertensive agents (except ACEIs, AIIRAs); candesartan vs. control: 25% vs. 16% on study drug only, 26% vs. 18% on study drug plus HCTZ 12.5mg baseline, 49% vs. 66% increase HCTZ or 12.5mg started after baseline, 17% vs. 26% beta-blocker, 18% vs. 28% CCB; respectively	Primary endpoint included major CV events (CV death, nonfatal MI, and nonfatal stroke); secondary endpoints included cognitive function (measured by MMSE), dementia, total mortality, CV mortality, fatal and non-fatal MI (combined and separate), fatal and non-fatal stroke (combined and separate), new onset DM, and discontinuation of study drug. Patients were followed-up at regular visits (1 and 3 months after randomization, then every 6 months)	Mean age 76 46% male, ethnicity not specified	4.5% previous MI, 3.9% previous stroke, 12% DM, education (10% less than primary school, 44% primary school, 40% more than primary school, 6% University)

Evidence Table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author Year Country Trial Name	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Lithell, 2003 U.S., Canada, Europe SCOPE trial (Fair)	Number screened not reported/4964 randomized/4937 enrolled	27 excluded/8 lost to fu/4937 analyzed	Primary endpoint first major CV event (CV death, nonfatal MI, non-fatal stroke): candesartan group vs. control risk reduction 10.9% (95% CI -6.0-25.1, P=0.19)

Evidence Table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author Year Country Trial Name	Results	Method of adverse effects assessment?	Adverse Effects Reported
Lithell, 2003 U.S., Canada, Europe SCOPE trial (Fair)	Secondary endpoints: risk of nonfatal stroke was reduced by 27.8% (95% CI 1.3-47.2, P=0.04) with candesartan vs. control; there was no significant difference in fatal, nonfatal or total MI, fatal stroke, CV mortality or total mortality; no significant difference in the adjusted change in MMSE score (decrease mean 28.5 to 28.0 with candesartan vs. 28.5 to 27.9 in the control group); no difference in cognitive decline or development of dementia; no difference in new-onset DM	Assessed at each visit (any unintended, unfavorable clinical sign or symptom, any illness or disease, or any clinically relevant deterioration in laboratory variable or other clinical test, whether or not considered treatment related)	Hypotension: candesartan (24.6%, 0.3% withdrew) vs. control (23.4%, 0.2% withdrew); dizziness/vertigo: candesartan (20.9%) vs. control (20.0%); accident/injury: candesartan (18.4%) vs. control (18.4%); back pain: candesartan (19.2%) vs. control (17.1%); bronchitis: candesartan (15.9%) vs. control (16.0%); sCr increased from 91.0 to 100.6umol/l with candesartan vs. 91.0 to 96.3 umol/l in the control group

Evidence Table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author Year Country Trial Name	Total withdrawals; withdrawals due to adverse events	Comments
Lithell, 2003 U.S., Canada, Europe SCOPE trial (Fair)	Total withdrawals not reported; candesartan vs. control: 15% vs. 17% withdrew due to adverse events	Originally designed as placebo-controlled trial. Mean dose candesartan 11.6±4.0mg/day; only 16% of patients in control group were on placebo (84% received open-label antihypertensive agents); mean BP 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)

Evidence Table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Parving, 2001 Canada, Europe, South America, South Africa (Fair)	Multicenter	Hypertensive patients, ranging in age from 30 to 70 years, with type 2 DM (WHO criteria), persistent microalbuminuria (defined as an albumin excretion rate of 20 to 200 µg/minute in 2 or 3 consecutive, sterile, overnight urine samples) and a sCr concentration of no more than 133 µmol/L for men and no more than 97 µmol/L for women; HTN was defined by the finding on at least 2 of 3 consecutive measurements obtained one week apart during the run-in period of a mean SBP > 135 mm Hg or mean DBP > 85 mm Hg or both	Irbesartan 150 mg once daily Irbesartan 300 mg once daily Placebo Duration 2 years	3-week run-in screening period during which all antihypertensive treatment was discontinued and replaced by placebo

Evidence Table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author Year Country Trial Name	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics
Parving, 2001 Canada, Europe, South America, South Africa (Fair)	Diuretics, beta blockers and nondihydropyridine CCBs	Clinic visits at weeks 2 and 4 and months 3, 6, 12, 18, 22, and 24	58 68.5% male 97.3% white	BMI 30.1 DM duration 9.7 years SBP 153 mm Hg DBP 90 mm Hg UAE 55.5 µg/min CrCl 109 ml/min

Evidence Table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author Year Country Trial Name	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Parving, 2001 Canada, Europe, South America, South Africa (Fair)	Number screened not reported/1469 eligible/611 enrolled	77(13.1%)/3(.5%)lost to fu/590 analyzed	**Primary endpoint** (time to onset diabetic nephropathy): Irbesartan150 9.7% Irbesartan300 5.2% Placebo 14.9% Irbesartan300 vs. placebo (HR 0.30 95% CI 0.14-0.61; P<0.001) NNT=8 (95% CI 5-19) Irbesartan150 vs. placebo (HR 0.61 95% CI 0.34-1.08; P=0.08) NNT=16 (95% CI 7-83)

Evidence Table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author Year Country Trial Name	Results	Method of adverse effects assessment?	Adverse Effects Reported
Parving, 2001 Canada, Europe, South America, South Africa (Fair)	<u>UAE</u> Placebo 2% decrease (P<0.0001 for placebo vs. combined irbesartan groups) Irbesartan150 24% decrease Irbesartan300 38% decrease <u>Restoration of normoalbuminuria</u> Placebo 21% Irbesartan150 24% Irbesartan300 34%(P=0.006 vs. placebo) <u>CrCl change at 24 months (estimated from graph)</u> Placebo 3.7% decrease Irbesartan150 5.4% decrease Irbesartan300 6.5% decrease NS	Not reported	<u>Serious adverse events</u> Placebo 22.8% Irbesartan150/300 15.4% (P=0.02) <u>Nonfatal CV events</u> Placebo 8.7% Irbesartan150 Not reported Irbesartan300 4.5% NS

Evidence Table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author Year Country Trial Name	Total withdrawals; withdrawals due to adverse events	Comments
Parving, 2001 Canada, Europe, South America, South Africa (Fair)	Total withdrawals Placebo 30/201(14.9%) Irbesartan150 27/195(13.8%) Irbesartan300 20/194(10.3%) Withdrawals due to adverse events Placebo 17/201(8.4%) Irbesartan150 18/195 (9.2%) Irbesartan300 8/194 (4.1%)	Average BP: placebo (144/83 mm Hg); irbesartan150 (143/83 mm Hg); irbesartan300 (141/83 mm Hg) (SBP P=0.0004 placebo vs. combined irbesartan groups)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial (Good)	RCT, multicenter	Age 55 to 80 with HTN (treated or untreated) and LVH (by ECG)	Losartan 50mg (with addition of HCTZ 12.5mg and subsequent titration to losartan 100mg) or atenolol 50mg (with addition of HCTZ 12.5mg and subsequent titration to atenolol 100mg) to achieve target BP < 140/90 mm Hg Mean follow-up 4.8 years

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial (Good)	1 to 2 weeks of placebo	HCTZ (as described under Interventions); addition of other antihypertensive agents (except ACEIs, AIIRAs, beta-blockers) allowed to achieve target BP (18% on losartan 50mg and 48% on 100mg required addition of HCTZ and/or other drugs; 20% on atenolol 50mg and 41% on 100mg required addition of HCTZ and/or other drugs)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial (Good)	Primary endpoint included CV morbidity and mortality (composite of CV death, MI, and stroke); secondary endpoints included total mortality, angina or HF hospitalization, coronary or peripheral revascularization, resuscitated cardiac arrest, new-onset DM. CV events were reviewed by an endpoint classification committee and deaths were reported to the data and safety monitoring board. Patients were followed-up at regular visits	Mean age 67 46% male, 92% white, 6% black, 1% Hispanic, 0.5% Asian	25% any vascular disease; 13% DM

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial (Good)	10,780 screened/9222 eligible/9193 enrolled	78 withdrawn/12 lost to fu/9193 analyzed	**Primary endpoint (composite CV mortality, MI, stroke):** losartan vs. atenolol adjusted HR 0.87 (95% CI 0.77-0.98; P=0.021), calculated NNT=56 (95% CI 32-217); when analyzed separately, fatal or nonfatal stroke adjusted HR 0.75 (95% CI 0.63-0.89; P=0.001) NNT=59 (95% CI 38-136) , no significant difference in CV death or MI

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial (Good)	**Secondary endpoints:** losartan vs. atenolol not significantly different except new onset DM adjusted HR 0.75 (95% CI 0.63-0.88; P=0.001)	Monitored throughout study; recorded at each visit on a worksheet	Hypotension: losartan (3%) vs. atenolol (2%) (P=0.001); cough: losartan (3%) vs. atenolol (2%); angioedema: losartan (0.1%) vs. atenolol (0.2%); bradycardia (P<0.0001), cold extremities (P<0.0001), sexual dysfunction (P=0.009) occurred more frequently with atenolol vs. losartan ; potassium was unchanged with losartan (0.0+0.4mmol/L) and decreased slightly with atenolol (0.1+0.5mmol/L)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial (Good)	Losartan vs. atenolol: 105/4605 (2.3%) vs. 92/4588 (2.0%) withdrew for any reason (1043/4605 (23%) losartan and 1243/4588 (27%) atenolol were off study drugs); approximately 13% on losartan vs. 18% on atenolol withdrew due to adverse events (P<0.0001)	At the end of the study, mean dose (mg/day): losartan 82+24, atenolol 79+26; Mean BP 144.1+17.1/81.3+9.6 mm Hg on losartan vs. 145.4+16.4/80.9+9.6 mm Hg on atenolol, adjustment for BP changes did not alter outcome

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease) (Good)	RCT, multicenter	Age 55 to 80 with HTN (treated or untreated) trough BP 160-200/95-115 mm Hg and LVH (by ECG); focus on patients without previous coronary, cerebral, or peripheral vascular disease	Losartan 50mg (with addition of HCTZ 12.5mg and subsequent titration to losartan 100mg) or atenolol 50mg (with addition of HCTZ 12.5mg and subsequent titration to atenolol 100mg) to achieve target BP < 140/90 mm Hg Mean follow-up 4.8 years

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease) (Good)	1 to 2 weeks of placebo	HCTZ (as described under Interventions); addition of other antihypertensive agents (except ACEIs, AIIRAs, beta-blockers) allowed to achieve target BP (19% on losartan 50mg and 49% on 100mg required addition of HCTZ or other drugs; 20% on atenolol 50mg and 43% on 100mg required addition of HCTZ or other drugs)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease) (Good)	Primary endpoint included CV morbidity and mortality (composite of CV death, MI, and stroke); secondary endpoints included total mortality, angina or HF hospitalization, coronary or peripheral revascularization, resuscitated cardiac arrest, new-onset DM. All events were reviewed by an endpoint classification committee. Patients were followed-up at regular visits	Mean age 66 44% male, 93% white, 5% black, 1% Hispanic, 0.6% Asian	11% DM; BP 174/98 mm Hg

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease) (Good)	10,780 screened/9222 eligible/6886 of 9193 enrolled in substudy	Number withdrawn not stated/none lost to fu before endpoint occurrence/6886 analyzed	**Primary endpoint (composite CV mortality, MI, stroke):** losartan vs. atenolol adjusted HR 0.81 (95% CI 0.69-0.95; P=0.008), NNT=53 (95% CI 31-187); when analyzed separately, fatal or nonfatal stroke adjusted HR 0.66 (95% CI 0.53-0.82; P<0.001) NNT=54 (95% CI 35-114), no significant difference in CV death or MI

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease) (Good)	**Secondary endpoints:** losartan vs. atenolol not significantly different except new onset DM adjusted HR 0.69 (95% CI 0.57-0.84; P<0.001)	Monitored throughout study; recorded at each visit on a worksheet	Any adverse event: losartan (12.7%) vs. atenolol (17.3%) (P<0.001); drug-related adverse event: losartan (6.0%) vs. atenolol (10.2%) (P<0.001); serious adverse event: losartan (3.8%) vs. atenolol (4.4%) (P>0.2); serious, drug-related adverse event: losartan (0.5%) vs. atenolol (1.0%) (P=0.018)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease) (Good)	Total withdrawals and withdrawals due to adverse events not specified; losartan 701/3402 (21%) and atenolol 866/3484 (25%) were off study drugs at the end of the trial	At the end of the study, mean dose (mg/day): losartan 82, atenolol 79; Mean BP 144.0/81.7 mm Hg on losartan vs. 145.1/81.4 mm Hg on atenolol, adjustment for BP as a time-varying covariate for the primary outcome (HR 0.822 (CI 0.684-0.988, P=0.037)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH) (Good)	RCT, multicenter	Age 55 to 80 with HTN (treated or untreated) trough BP 160-200/< 90 mm Hg and LVH (by ECG)	Losartan 50mg (with addition of HCTZ 12.5mg and subsequent titration to losartan 100mg) or atenolol 50mg (with addition of HCTZ 12.5mg and subsequent titration to atenolol 100mg) to achieve target BP < 140/90 mm Hg Mean follow-up 4.7 years

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH) (Good)	1 to 2 weeks of placebo	HCTZ (as described under Interventions); addition of other antihypertensive agents (except ACEIs, AIIRAs, beta-blockers) allowed to achieve target BP (20.6% on losartan 50mg and 41.8% on 100mg required addition of HCTZ and/or other drugs; 22.2% on atenolol 50mg and 35.4% on 100mg required addition of HCTZ and/or other drugs)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH) (Good)	Primary endpoint included CV morbidity and mortality (composite of CV death, MI, and stroke); secondary endpoints included total mortality, angina or HF hospitalization, coronary or peripheral revascularization, resuscitated cardiac arrest, new-onset DM. Findings of the primary outcome were confirmed with an on-treatment approach that censored end points from patients 14 days after the drug was discontinued. Patients were followed-up at regular visits	Mean age 70 40% male, 92% white, 6% black, 1% Hispanic, 0.5% Asian	DM: 15.6% losartan, 19.8% atenolol; CHD: 23.9% losartan, 21% atenolol; CVD: 10.6% losartan, 12.9% atenolol; BP 174/83 mm Hg

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH) (Good)	10,780 screened/9222 eligible/1326 of 9193 enrolled in substudy	14 withdrawn/2 lost to fu/1326 analyzed	**Primary endpoint (composite CV mortality, MI, stroke):** losartan vs. atenolol adjusted RR 0.75 (95% CI 0.56-1.01; P=0.06), unadjusted RR 0.71 (95% CI 0.53-0.95; P=0.02), NNT=24 (95% CI 14-172); when analyzed separately, fatal or nonfatal stroke adjusted RR 0.60 (95% CI 0.38-0.92; P=0.02) NNT=28 (95% CI 16 - 112); CV mortality adjusted RR 0.54 (95% CI 0.34-0.87; P=0.01) NNT=27 (95% CI 16-85); no significant difference in MI

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH) (Good)	**Secondary endpoints:** losartan vs. atenolol not significantly different except new onset DM adjusted HR 0.62 (95% CI 0.40-0.97; P=0.04) and total mortality adjusted HR 0.72 (95% CI 0.53-1.00; P=0.046)	Monitored throughout study; recorded at each visit on a worksheet	Hypotension: losartan (4.4%) vs. atenolol (2.7%); cough: losartan (4.1%) vs. atenolol (2.9%); angioedema: losartan (0.3%) vs. atenolol (0.3%); bradycardia (P<0.001), cold extremities (P=0.05) occurred more frequently with atenolol vs. losartan; potassium decreased slightly with losartan (-0.002mEq/L) and with atenolol (-0.08mEq/L)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH) (Good)	Losartan vs. atenolol: 9 and 5 withdrew consent (169/660 (25.5%) losartan and 216/666 (32.3%) atenolol discontinued therapy); 14.6% on losartan vs. 22.1% on atenolol discontinued therapy due to an adverse event (P<0.001); 7.1% on losartan vs. 13.5% on atenolol discontinued due to drug-related adverse event (P<0.001)	At the end of the study, mean dose (mg/day): losartan 79, atenolol 76; Mean BP 146/75 mm Hg on losartan vs. 146/74 mm Hg on atenolol (DBP P=0.04), adjustment for BP did not alter outcome

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM) (Good)	RCT, multicenter	Age 55 to 80 with HTN (treated or untreated) trough BP 160-200/< 90 mm Hg and LVH (by ECG), DM (most likely type 2 per study)	Losartan 50mg (with addition of HCTZ 12.5mg and subsequent titration to losartan 100mg) or atenolol 50mg (with addition of HCTZ 12.5mg and subsequent titration to atenolol 100mg) to achieve target BP < 140/90 mm Hg Mean follow-up 4.7 years

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM) (Good)	1 to 2 weeks of placebo	HCTZ (as described under Interventions); addition of other antihypertensive agents (except ACEIs, AIIRAs, beta-blockers) allowed to achieve target BP (14% on losartan 50mg and 50% on 100mg required addition of HCTZ and/or other drugs; 16% on atenolol 50mg and 46% on 100mg required addition of HCTZ and/or other drugs)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM) (Good)	Primary endpoint included CV morbidity and mortality (composite of CV death, MI, and stroke); secondary endpoints included total mortality, angina or HF hospitalization, coronary or peripheral revascularization, resuscitated cardiac arrest. Findings of the primary outcome were confirmed by an endpoint committee. Patients were followed-up at regular visits	Mean age 67 47% male, 86% white, 11% black, 2% Hispanic, 0.8% Asian	35% any vascular disease; current smokers: 12% losartan, 15% atenolol; BP 177/96 mm Hg

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM) (Good)	10,780 screened/9222 eligible/1195 of 9193 enrolled in substudy	18 withdrew consent/4 lost to fu/1195 analyzed	**Primary endpoint (composite CV mortality, MI, stroke):** losartan vs. atenolol adjusted HR 0.76 (95% CI 0.58-0.98; P=0.031), NNT=19 (95% CI 10-141); when analyzed separately, CV mortality adjusted HR 0.63 (95% CI 0.42-0.95; P=0.028) NNT=28 (95% CI 15-236); no significant difference in fatal or nonfatal stroke, or MI

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM) (Good)	**Secondary endpoints:** losartan vs. atenolol not significantly different except total mortality adjusted HR 0.61 (95% CI 0.45-0.84; P=0.002); HF hospitalization adjusted HR 0.59 (95% CI 0.38-0.92; P=0.019)	Monitored throughout study; recorded at each visit on a worksheet	Hypotension: losartan (2%) vs. atenolol (1%); cough: losartan (4%) vs. atenolol (3%); angioedema: losartan (0.2%) vs. atenolol (0.5%); bradycardia (P<0.0001) occurred more frequently with atenolol vs. losartan; potassium increased slightly with losartan (0.05mmol/L) and was unchanged with atenolol; glucose increased slightly with both losartan and atenolol (0.05mmol/L)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM) (Good)	Losartan vs. atenolol: 0 and 4 withdrew consent (159/586 (27%) losartan and 194/609 (32%) atenolol discontinued therapy); 0.3% on losartan vs. 2% on atenolol discontinued therapy due to a serious drug-related adverse event (P=0.065)	Mean BP at last visit before primary endpoint or at end of study 146/79 mm Hg on losartan vs. 148/79 mm Hg on atenolol, adjustment for BP had little effect (data not shown). Open-label AIIRA or ACEI allowed after study drug discontinued

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial (Good)	RCT, multicenter	Men and women > 18 years of age AMI (within 0.5 to 10 days) complicated by clinical or radiologic signs of HF, LV systolic dysfunction (EF < 0.35 on ECHO or contrast angiography and < 0.40 on radionuclide ventriculography), or both SBP > 100 mm Hg sCr < 2.5mg/dl	Titration by 3 months to: valsartan 160mg twice daily vs. valsartan 80mg twice daily + captopril 50mg three times daily vs. captopril 50mg three times daily (medication adjusted at investigator's discretion) Mean follow-up 2.1 years	None

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial (Good)	ACEI or AIIRA up to 12 hours prior to randomization Baseline: beta-blockers (70%); aspirin (91%)	Primary endpoint was all-cause mortality; clinical status, study outcomes (Definitions of End Points available in Supplementary Index 1. at www.nejm.org); drug tolerance, quality of life, pharmacoeconomic variables assessed at each visit (i.e., 6 times during first year, then at 4 month intervals for the duration of the trial)	Mean age 65 69% male, 93.5% white, 2.8% black, 1% Asian, 2.8% other

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial (Good)	35.3% LVEF, 28% previous MI, 49% Killip class II, 15% HF, 7% CABG, 7.2% PCI, 6% stroke	Number screened not reported/number eligible not reported/14,808 enrolled	105 information censored due to informed-consent process at one site/139 vital status unavailable (55 of these withdrew consent)/14,703 analyzed

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Results	Results	Method of adverse effects assessment?
Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial (Good)	**Primary endpoint (all-cause mortality):** valsartan vs. captopril: HR 1.00 (97.5% CI 0.90-1.11; P=0.98); valsartan + captopril vs. captopril: HR 0.98 (97.5% CI 0.89-1.09; P=0.73); mortality at one year estimates: 12.5% valsartan, 12.3% valsartan + captopril, 13.3% captopril	**Secondary endpoints:** valsartan vs. captopril: combined CV mortality and MI, or HF HR 0.95 (97.5% CI 0.88-1.03; P=0.20); P<0.001 for non-inferiority; valsartan + captopril vs. captopril: combined CV mortality and MI, or HF HR 0.97 (97.5% CI 0.89-1.05; P=0.37); additional comparisons of CV mortality and morbidity not statistically significant	Elicited by investigator at study visit

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial (Good)	hypotension: valsartan (15.1%) vs. valsartan + captopril (18.2%) vs. captopril (11.9%) decreased dose (P<0.05 valsartan vs. captopril, valsartan + captopril vs. captopril); valsartan (1.4%) vs. valsartan + captopril (1.9%) vs. captopril (0.8%) discontinued treatment (P<0.05 valsartan vs. captopril, valsartan + captopril vs. captopril) cough: valsartan (1.7%) vs. valsartan + captopril (4.6%) vs. captopril (5.0%) decreased dose (P<0.05 valsartan vs. captopril); valsartan (0.6%) vs. valsartan + captopril (2.1%) vs. captopril (2.5%) discontinued treatment (P<0.05 valsartan vs. captopril)	renal causes: valsartan (4.9%) vs. valsartan + captopril (4.8%) vs. captopril (3.0%) decreased dose (P<0.05 valsartan vs. captopril, valsartan + captopril vs. captopril); valsartan (1.1%) vs. valsartan + captopril (1.3%) vs. captopril (0.8%) discontinued treatment (P<0.05 valsartan + captopril vs. captopril) hyperkalemia: valsartan (1.3%) vs. valsartan + captopril (1.2%) vs. captopril (0.9%) decreased dose; valsartan (0.1%) vs. valsartan + captopril (0.2%) vs. captopril (0.1%) discontinued treatment angioedema: valsartan (0.2%) vs. valsartan + captopril (0.5%) vs. captopril (0.5%) decreased dose; valsartan (0.2%) vs. valsartan + captopril (0.2%) vs. captopril (0.3%) discontinued treatment	valsartan vs.valsartan + captopril vs. captopril: 1001/4885 (20.5%) vs. 1139/4862 (23.4%) vs. 1055/4879 (21.6%) discontinued treatment for any reason (P<0.05 valsartan + captopril vs. captopril); valsartan vs.valsartan + captopril vs. captopril: 282/4885 (5.8%) vs. 438/4862 (9.0%) vs. 375/4879 (7.7%) discontinued treatment due to adverse events (P<0.05 valsartan vs. captopril, valsartan + captopril vs. captopril)

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Comments
Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial (Good)	Pre-specified tests for noninferiority for valsartan vs. captopril showed that the upper limit of one-sided 97.5% CI was in the specified margin for noninferiority (P=0.004 intention-to-treat analysis; P=0.002 per-protocol analysis). The effect of valsartan was estimated to be 99.6% of captopril (95% CI 60 to 139). At 1 year, mean dose (mg/day): valsartan 247 + 105, valsartan 116 + 53 + captopril 107 + 53, captopril 117 + 49; target dose: valsartan 56%, valsartan + captopril 47%, captopril 56% Mean SBP: 2.2 mm Hg lower valsartan + captopril vs. captopril (P<0.001); 0.9 mm Hg lower valsartan vs. captopril (P<0.001)

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAL trial (Good)	RCT, multicenter	Men and women > 50 years of age with documented AMI and signs or symptoms of HF during the acute phase or new Q-wave anterior infarction or reinfarction	Losartan 12.5mg daily, titrated to 50mg daily vs. captopril 12.5mg three times daily, titrated to 50mg three times daily Mean follow-up 2.7 years	None

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	
Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAL trial (Good)	Baseline: beta-blockers (79%); aspirin (95%); thrombolytic (54%)	Primary (all-cause mortality), secondary, and tertiary endpoints and fatal or nonfatal stroke were adjudicated by the endpoint committee. Causes for hospital admission were determined by the investigator. Safety and tolerability assessment included discontinuations due to adverse events and prespecified adverse events. Biochemical test were preformed at a core laboratory and health-related quality-of-life was assessed	Mean age 67 98.5% white	71% male,

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAL trial (Good)	18% previous MI, 57% Killip class II, 6% HF, 2.5% CABG, 3.4% stroke	31,738 screened/number eligible not reported/5477 enrolled	1082 withdrawn/1 lost to follow-up/5477 analyzed

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Results	Results	Method of adverse effects assessment?
Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAL trial (Good)	**Primary endpoint (all-cause mortality):** losartan vs. captopril: RR 1.13 (95% CI 0.99-1.28; P=0.069)	**Secondary endpoints:** losartan vs. captopril: sudden cardiac death or resuscitated cardiac arrest RR 1.19 (95% CI 0.99-1.43; P=0.072); fatal or nonfatal reinfarction RR 1.03 (95% CI 0.89-1.18; P=0.722)	Monitored

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAL trial (Good)	hypotension: losartan (13.3%) vs. captopril (16.3%); cough: losartan (9.3%) vs. captopril (18.7%) (P<0.0001), discontinued treatment (P<0.0001 losartan vs. captopril); angioedema: losartan (0.4%) vs. captopril (0.8%), discontinued treatment (P=0.019 losartan vs. captopril)	skin rash: losartan (3.1%) vs. captopril (4.6%) (P=0.005), discontinued treatment (P=0.0008 losartan vs. captopril); taste disturbance: losartan (0.6%) vs. captopril (2.7%) (P<0.0001), discontinued treatment (P<0.0001 losartan vs. captopril); significant difference losartan vs. captopril in change from baseline for serum uric acid (49.6*u* mol/L vs. 60.8*u* mol/L, respectively P=0.01) and serum potassium (0.19mmol/L vs. 0.22mmol/L, respectively P=0.01)	losartan vs.captopril: 458/2744 (17%) vs. 624/2733 (23%) discontinued treatment for any reason (P<0.0001); 202/2744 (7%) vs. 387/2733 (14%) discontinued treatment due to adverse events (P<0.0001)

Evidence Table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

Author Year Country Trial Name (Quality Score)	Comments
Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAL trial (Good)	Results did not show superiority or noninferiority for losartan compared to captopril. If losartan had demonstrated noninferiority, this would have also implied that losartan is superior to placebo. This assumption could not be made from the results of the trial. Mean dose at end of trial: losartan 45 + 12mg daily, captopril 44 + 12mg three times daily; target dose at 1 month: losartan 71%, captopril 70%. Mean SBP/DBP were lower at 1 hour with captopril vs. losartan (P<0.0001), otherwise recorded blood pressures were similar

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	RCT, multicenter	Men and women > 60 years of age (85% > 65 years), NYHA class II-IV HF and LVEF < 40% on ECHO or radionuclear ventriculography), no previous ACEI or AIIRA use (unless length of therapy < 7 days within 3 months prior to randomization)	Titration at weekly intervals: losartan 12.5mg once daily, then 25mg, up to 50mg once daily vs. captopril 12.5mg three times daily, then 25mg, up to 50mg three times daily Mean follow-up 1.5 years
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	RCT, multicenter	Age > 65 years, NYHA class II-IV HF and LVEF < 40%, no previous ACEI use	Titration at weekly intervals: losartan 12.5mg once daily, then 25mg, up to 50mg once daily (with placebo for captopril) vs. captopril 6.25mg three times daily, then 25mg, up to 50mg three times daily (with placebo for losartan) Follow-up 48 weeks

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	Single-blind placebo run-in of 1 to 28 days (matched to losatan or captopril tablets) for patient assessment and clinical stability, and to ensure adherence	All treatments allowed except for open-label ACEIs or AIIRAs Baseline: beta-blockers (22%); ACEIs (23%)
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	2 week placebo run-in	All CV treatments allowed except for open-label ACEIs Baseline: beta-blockers (16%); non-ACEI vasodilators (40%)

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	Primary endpoint (all-cause mortality), secondary endpoint (composite sudden cardiac death or resuscitated cardiac arrest); clinical assessment every 4 months, laboratory assessments at 1 month then every 4 months, study outcomes reviewed and classified by independent clinical endpoint committee	Mean age 71.5 70% male, 82% white, 2% black, 5% Asian, 11% other
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	Primary endpoint included renal dysfunction (increase sCr by > 26.5umol/L or > 0.3mg/dl from baseline, confirmed by repeat 5-14 days later); secondary endpoints included all-cause mortality and HF hospitalizations (composite all-cause mortality and HF hospitalizations added as protocol amendment); additional prespecified endpoints included worsening HF (NYHA functional class); clinical assessment every 3 months, laboratory assessments at 3, 6, 12 weeks and then every 3 months; study outcomes reviewed and classified by independent clinical endpoint committee	Mean age 74 67% male, 90% white, 5% black

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	31% LVEF, 58% previous MI, 79% ischemia, 52% NYHA class II and 43% class III, 49% HTN	Number screened not reported/number eligible not reported/3152 enrolled	530 died/346 withdrawn/2 lost to fu/3152 analyzed
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	31% LVEF, 50% previous MI, 68% HF due to IHD, 65% NYHA class II, 34% class III, 2% class IV, 57% HTN	Number screened not reported/number eligible not reported/722 enrolled	176 withdrawn/number lost to fu not reported/722 analyzed

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Results	Results
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	**Primary endpoint (all-cause mortality):** losartan vs. captopril: 17.7% vs 15.9% HR 1.13 (95.7% CI 0.95-1.35; P=0.16) average annual mortality rate: 11.7% losartan, 10.4% captopril	**Secondary endpoints:** losartan vs. captopril: sudden death or resuscitated cardiac arrest HR 1.25 (95% CI 0.98-1.60; P=0.08); combined total mortality or hospital admission for any reason HR 1.07 (95% CI 0.97-1.19; P=0.18); hospital admissions HR 1.04 (95% CI 0.94-1.16; P=0.45); hospital admissions for HF HR 0.92 (95% CI 0.78-1.08; P=0.32)
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	**Primary endpoint (change in baseline sCr):** % increase in serum creatine: Losartan: 10.5% Captopril: 10.5% Additional prespecified endpoints: NYHA functional class (% class I or II): Losartan: baseline=66% end of study=80% Captopril: baseline=64% end of study=81% P<0.001	**Secondary endpoints:** all-cause mortality: Losartan: 4.8% Captopril: 8.7% RR (95% CI) = 0.46 (0.05-0.69) P=0.035 HF hospitalizations: Losartan: 5.7% Captopril: 5.7% RR (95% CI) = 0.04 (-0.74-0.47) P=0.89 composite all-cause mortality and HF hospitalizations: Losartan: 9.4% Captopril: 13.2% RR (95% CI) = 0.32 (-0.04-0.55) P=0.075

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	Not reported	Withdrawals due to cough: losartan vs. captopril ~1% vs. ~3% (P<0.001); worsening HF (25% each group)	losartan vs. captopril: 125/1578 (7.9%) vs. 221/1574 (14.0%) discontinued treatment for any reason; ~10% vs. ~15% (P<0.001) discontinued treatment due to any adverse effect; ~3% vs. ~8% (P<0.001) discontinued treatment due to drug-related adverse effect
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	Not reported	Withdrawals due to cough: losartan 0/352 (0%) vs. captopril 14/370 (3.8%) (P<0.002); withdrawals due to angioedema: losartan 0/352 (0%) vs. captopril 3/370 (0.8%); withdrawals due to hyperkalemia: losartan 2/352 (0.6%) vs. captopril 6/370 (1.6%); persisting increases in serum potassium > 0.5mmol/L vs. baseline occurred in 18.8% on losartan and 22.7% on captopril (P=0.069)	losartan vs. captopril: 65/352 (18.5%) vs. 111/370 (30.0%) (P<0.001) discontinued treatment for any reason or died; 43/352 (12.2%) vs. 77/370 (20.8%) discontinued treatment due to any adverse event (excluding death) (P<0.002)

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Comments
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	ELITE II was designed as a superiority trial therefore cannot draw any conclusions about equivalence. The superiority of losartan vs. captopril in reducing mortality (not the primary endpoint) seen in ELITE were based on a small number of deaths, ELITE II had 10 times more events and 4 times more patients. For patients on beta-blockers at baseline losartan vs. captopril HR death 1.77 (those without beta-blockers HR 1.05), difference not noted for patients on concomitant therapy throughout the study. Patients randomized according to baseline beta-blocker use. No significant difference in heart rate or BP lowering per last measurement of treatment
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	85% patients on losartan achieved target dose (mean 42.6mg) compared to 71% on captopril (mean 122.7mg). Authors report the difference in discontinuation rate did not account for 46% difference in total mortality as the difference was seen predominately in patients who continued on treatment (losartan 11/298 or 3.7% vs. captopril 24/282 or 57%)

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Houghton, 1999 U.K. ELITE Trial substudy (Fair)	RCT	Age > 65 years, NYHA class II-IV HF and LVEF < 40%, no previous ACEI use	Titration at weekly intervals: losartan 12.5mg once daily, then 25mg, up to 50mg once daily (with placebo for captopril) vs. captopril 6.25mg three times daily, then 25mg, up to 50mg three times daily (with placebo for losartan) Follow-up 24 weeks
Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	RCT, multicenter	Age > 65 years, NYHA class II-IV HF and LVEF < 40%, no previous ACEI use, English speaking with access to a phone and able to use the phone to answer questions	Titration at weekly intervals: losartan 12.5mg once daily, then 25mg, up to 50mg once daily (with placebo for captopril) vs. captopril 6.25mg three times daily, then 25mg, up to 50mg three times daily (with placebo for losartan) Follow-up 48 weeks
Willenheimer, 2002 Sweden HEAVEN Study (Fair)	RCT, multicenter	Males and females > 18 years, stable HF, NYHA class II-III and LVEF < 45%, on ACEI for > 3 months, able to perform 6-min-walk test	Valsartan 80mg once daily titrated after 1 week to 160mg once daily vs. enalapril 5mg twice daily titrated after 1 week to 10mg twice daily Follow-up 12 weeks

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Houghton, 1999 U.K. ELITE Trial substudy (Fair)	2 week placebo run-in	All CV treatments allowed Baseline: diuretics (90%); no patients on beta-blockers
Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	2 week placebo run-in	All CV treatments allowed Baseline medications not specified
Willenheimer, 2002 Sweden HEAVEN Study (Fair)	2 week placebo run-in	All other medications kept stable if possible Baseline: ACEIs (100%), beta-blockers (77%)

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Houghton, 1999 U.K. ELITE Trial substudy (Fair)	One of the primary endpoints included exercise capacity as measured by a pair of hip-borne pedometers provided to the patient for periods of 2 weeks to assess activity at home; also assessed by 100 m corridor walk test at self-selected slow, normal, and fast speeds. Patients were evaluated at baseline (placebo run-in visit) and at 12 and 24 weeks	Mean age 73 ethnicity not specified 78% male,
Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	Main objective to measure health related QOL using two instruments, the disease specific Minnesota Living with Heart Failure (LIhFE) and a more general Sickness Impact Profile (SIP) administered at baseline (within 7 days prior to randomization) and after 12 and 48 weeks of double-blind therapy	Mean age 74 88% white, 10% black 76% male,
Willenheimer, 2002 Sweden HEAVEN Study (Fair)	Primary endpoint included exercise capacity (6-min-walk test) assessed at -2, 0, 6, and 12 weeks; secondary endpoints included clinical status (dyspnea-fatigue index DFI) that describes severity of symptoms (0=worst, 12=no symptoms) and QOL (Minnesota Living with Heart Failure Questionnaire MLWHFQ) using 20 of 21 questions (worst score=100), both assessed at 0 and 12 weeks	Mean age 68 ethnicity not specified 75% male,

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Houghton, 1999 U.K. ELITE Trial substudy (Fair)	23% LVEF, 61% HF due to IHD, 94% NYHA class II, 6% class III	Number screened not reported/number eligible not reported/18 enrolled	4 withdrawn/number lost to fu not reported/number analyzed not specified in results for exercise capacity
Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	30% LVEF, 68% HF due to IHD, 63% NYHA class II, 37% class III/IV	Number screened not reported/300 eligible/278 enrolled	75 discontinued early from trial (30/147 losartan; 45/153 captopril)/29 lost to fu, withdrawn, or protocol violation/203 complete data available
Willenheimer, 2002 Sweden HEAVEN Study (Fair)	61% HF due to IHD, 71% NYHA class II, 29% class III	Number screened not reported/146 enrolled/141 randomized	14 withdrawn/number lost to fu not reported/134 analyzed for ITT primary endpoint; 118 analyzed for per protocol population

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Results	Results
Houghton, 1999 U.K. ELITE Trial substudy (Fair)	**One of primary endpoints (exercise capacity):** corridor walk time: pedometer scores: mean score (sem) Losartan: baseline=28980 (4862) week 12=27851 (4987) week 24=28073 (6473) Captopril: baseline=28639 (6372) week 12=29474 (6390) week 24=30496 (5777)	
Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	**Main objective (HRQOL):** LIhFE (mean change from baseline (sem)): Losartan=-9 (2.5) P=0.586 Captopril=-11 (2.5) P=0.414 SIP: (mean change from baseline (sem)): Losartan=-2.7 (0.5) P=0.689 Captopril=-3 (1) P=0.982	
Willenheimer, 2002 Sweden HEAVEN Study (Fair)	**Primary endpoint (exercise capacity):** 6-min-walk test: mean (sd) in minutes Valsartan: baseline=418.2(112.9) 6 weeks=419.3(115.9) 12 weeks=423.7(118.7) Enalapril: baseline=424(115.1) 6 weeks=437.6(106.2) 12 weeks=423.7(113.7)	**Secondary endpoint (exercise capacity):** DFI: LSM change (se) Valsartan=0.24 (0.16) Enalapril=0.26 (0.16) MLWHFQ: LSM change (se) Valsartan=0.7 (1.3) Enalapril=0.9 (1.3)

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Houghton, 1999 U.K. ELITE Trial substudy (Fair)	Not reported	Not reported	4 withdrawals in the captopril group (none in the losartan group)/3 withdrawals following adverse clinical events; 1 patient died
Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	Not reported	Not reported	75 total withdrawals (30/147 losartan; 45/153 captopril)/46 withdrawals (losartan 16/147 or 10.9% vs. captopril 29/153 or 19.0% for unfavorable reasons (death, clinical or laboratory adverse events)
Willenheimer, 2002 Sweden HEAVEN Study (Fair)	Adverse events recorded at all visits	All adverse events: valsartan 35/70 (50%) vs. enalapril 45/71 (63%); headache: valsartan 4/70 (5.7%) vs. enalapril 1/71 (1.4%); diarrhea: valsartan 3/70 (4.3%) vs. enalapril 2/71 (2.8%); dizziness: valsartan 3/70 (4.3%) vs. enalapril 6/71 (8.5%)	14 total withdrawals including death (valsartan 5/70 or 7.1% vs. enalapril 9/71 or 12.7%)/5 withdrawals due to adverse events (2 valsartan; 3 enalapril)

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Comments
Houghton, 1999 U.K. ELITE Trial substudy (Fair)	Methods state sample size gave study power of 75% to detect 15% difference in corridor walk time at P=0.05
Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	After unblinding in ELITE, composite statistical approach used for HRQOL to account for differential dropout rates (noted that higher withdrawal rate with captopril due to adverse events or death and lack of QOL data at time of discontinuation may impact analysis)
Willenheimer, 2002 Sweden HEAVEN Study (Fair)	Patients stabilized on ACEI prior to inclusion

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Dunselman, 2001 Europe REPLACE (Fair)	RCT, multicenter	Age > 21 years, ambulatory, chronic moderate symptomatic HF, NYHA class II-III and LVEF < 40%, in sinus rhythm, stable on enalapril 10mg twice daily and diuretic (+ digoxin) for 28 days prior to randomization	Telmisartan 10, 20, 40, or 80mg once daily vs. enalapril 10mg twice daily Follow-up 12 weeks
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Poor)	RCT, multicenter	NYHA class II, III, or IV HF, 6-min-walk distance (6MWD) < 500m, LVEF < 40%	Candesartan 4, 8, or 16mg once daily vs. enalapril 10mg twice daily vs. candesartan 4 or 8mg once daily plus enalapril 10mg twice daily Follow-up 43 weeks

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Dunselman, 2001 Europe REPLACE (Fair)	Screening phase on enalapril 10mg twice daily and diuretic (+ digoxin) for 28 days	Long-acting nitrates, hydralazine, prazosin, beta-blockers, anticoagulants, antiplatelet agents Baseline: digoxin (39%), utilization of other baseline medications not specified
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Poor)	Three phases (each 1 week duration): enalapril 2.5mg twice daily plus placebo candesartan; enalapril 2.5mg twice daily plus candesartan 2mg daily; enalapril 2.5mg twice daily plus placebo candesartan	Medications for HF Baseline: diuretics (84%), digoxin (71%), beta-blockers (14% candesartan group, 13% combination group, 23% enalapril group; P<0.05 both vs. enalapril group) At 19 weeks, eligible patients (without contraindications and did not refuse therapy) were randomized to metoprolol or placebo

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Dunselman, 2001 Europe REPLACE (Fair)	Primary endpoint included bicycle exercise duration (upright sitting position using bicycle exercise test protocol 2hrs after morning medications) assessed at least twice during screening and at 4 and 12 weeks; secondary endpoints included NYHA functional class (assessed at screening and during treatment), QOL (Minnesota Living with Heart Failure Questionnaire MLHF) assessed at screening and after 4 and 12 weeks of treatment	Mean age 65 89% male, ethnicity not specified
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Poor)	Endpoints included change from baseline in 6MWD (performed in duplicate), NYHA functional class, and QOL (Minnesota Living with Heart Failure Questionnaire) assessed at weeks 17 or 18 and week 43	Mean age 63 85% male, ethnicity not specified

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Dunselman, 2001 Europe REPLACE (Fair)	26% LVEF, 78% HF due to IHD, 64% NYHA class II, 36% class III	Number screened not reported/number eligible not reported/378 enrolled	11 withdrawn/number lost to fu not reported/367 analyzed for primary endpoint; 378 analyzed for safety
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Poor)	27% LVEF, 72% HF due to IHD, 63% NYHA class II, 35% class III, 2% class IV	Number screened not reported/899 eligible/768 enrolled	Number withdrawn not reported/number lost to fu not reported/768 analyzed

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Results	Results
Dunselman, 2001 Europe REPLACE (Fair)	**Primary endpoints (exercise capacity):** bicycle exercise duration: mean (sd) exercise duration (s) relative to enalapril: Telmisartan10 mg = 7.2 (16) Telmisartan 20 mg = 6.8 (15) Telmisartan 40 mg = 0.8 (14) Telmisartan 80 mg = 5.7 (16)	**Secondary endpoint (exercise capacity):** MLHF: Replacement of enalapril by any dose of telmisartan studies did not significantly affect the total MLHF score. NYHA functional class: There were no significant changes detected for any group in NYHA classification.
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Poor)	**Endpoints (exercise capacity):** 6MWD: mean (se) at baseline and follow-up in m Candesartan: baseline=379 (5) follow-up=390 (6) Candesartan/Enalapril: baseline=386 (5) follow-up=385 (6) Enalapril: baseline=374 (8) follow-up=387 (11)	**Endpoints:** NYHA functional class: No significant differences between groups QOL (Minnesota Living with Heart Failure Questionnaire): No significant differences between groups

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Dunselman, 2001 Europe REPLACE (Fair)	Monitored vital signs and laboratory tests at 4 and 12 weeks; 12 lead ECG before each exercise test and 24hr Holter ECG at baseline and 12 weeks; type, onset, duration, intensity, treatment required, outcome, relationship to study drug, documented for all adverse events during study; serious adverse events were fatal, life-threatening, disabling, or requiring prolonged hospital stay	Cough: telmisartan 9/301 (3%) vs. enalapril 4/71 (5.6%) (P=0.3)	11 withdrawals for protocol violations (4 telmisartan 10mg; 2 telmisartan 40mg; 3 telmisartan 80mg; 2 enalapril 20mg)/9 withdrawals due to adverse events (6 withdrawals due to death: 2 telmisartan 20mg, 1 telmisartan 40mg, 1 telmisartan 80mg, 2 enalapril 20mg; 3 withdrawals due to adverse events with telmisartan)
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Poor)	Not reported	Potassium: candesartan -0.23+0.03 mmol/L vs. enalapril -0.01+0.05 mmol/L (P<0.05) at 43 weeks; vs. candesartan plus enalapril 0.11+0.03 mmol/L (P<0.05) at 43 weeks	Total withdrawals not reported/withdrawals due to adverse events not reported

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Comments
Dunselman, 2001 Europe REPLACE (Fair)	Patients stabilized on ACEI prior to inclusion
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Poor)	Pilot trial. Study terminated 6 weeks early due to concern by External Safety and Efficacy Monitoring Committee [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)] although not powered to assess morbidity and mortality

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Lang, 1997 U.S., Canada (Fair)	RCT, multicenter	Symptomatic HF, NYHA class II-IV and LVEF < 45%, received stable doses of an ACEI for 6 weeks and a diuretic for 2 weeks	Losartan 12.5mg, titrated as tolerated to 25mg daily vs. losartan 12.5mg, titrated as tolerated to 25mg, then 50mg daily vs.enalapril 2.5mg titrated as tolerated to 5mg, then 10mg twice daily Follow-up 12 weeks
Dickstein, 1995 Scandinavia (Fair)	RCT, multicenter	Symptomatic HF, stabilized on an ACEI	Losartan 12.5mg, titrated as tolerated to 25mg or 50mg once daily vs. enalapril 2.5mg titrated as tolerated sequentially to 5 and 10mg twice daily (placebo tablets provided to secure blinding due to different dosage intervals) Follow-up 8 weeks

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Lang, 1997 U.S., Canada (Fair)	After screening visit, placebo in additional to stable ACEI and diuretic for 3 visits (time period not specified) during baseline exercise period; open-label ACEI discontinued prior to randomization	Digoxin (dose stable for previous 2 weeks), non-ACEI vasodilators (dose stable for previous 6 weeks) Baseline: digoxin (85%), beta-blockers (10.5% losartan 25mg group, 2.5% losartan 50mg group, 7.9% enalapril group), other vasodilators (34.2% losartan 25mg group, 55% losartan 50mg group, 60.5% enalapril group; P<0.05 losartan 25mg vs. enalapril)
Dickstein, 1995 Scandinavia (Fair)	Three week placebo run-in while on stable ACEI doses	Diuretic and digoxin doses kept stable if possible Baseline: digoxin (63%), beta-blockers (19% losartan 25mg group, 11% losartan 50mg group, 7% enalapril group; difference not statistically significant)

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Lang, 1997 U.S., Canada (Fair)	Endpoints included change from baseline in symptom-limited treadmill exercise duration (patients randomized to "treadmill patient" if completed 2 consecutive baseline treadmill tests where exercise duration did not differ by more than 10% or "non-treadmill patient") assessed at 6, 11, and 12 weeks post-randomization, 6-min walk test assessed at 6, 9, and 12 weeks post-randomization, dyspnea-fatigue index assessed at 6, and 12 weeks post-randomization, and signs and symptoms of HF (dyspnea, PND, orthopnea, jugular venous pressure, peripheral edema, pulmonary rales, and third heart sound), and NYHA functional class	Mean age 58 78% male, 71% white, 22% black, 5% Hispanic, 3% Asian
Dickstein, 1995 Scandinavia (Fair)	Primary endpoints included assessment of exercise capacity (change from baseline in 6-min walk test and dyspnea-fatigue index, both assessed at 8 weeks with average of last two baseline tests was used as baseline measurement), and clinical status (dyspnea, PND, orthopnea, jugular venous pressure, peripheral edema, pulmonary rales, and third heart sound), and NYHA functional class assessed at baseline and weeks 1, 2, 3, 4, 6 and 8	Mean age 64 77% male, ethnicity not specified

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Lang, 1997 U.S., Canada (Fair)	47% HF due to IHD, 47% NYHA class II, 51% class III, 2% class IV	Number screened not reported/number eligible not reported/116 enrolled	Number withdrawn not reported/number lost to fu not reported/number analyzed not specified
Dickstein, 1995 Scandinavia (Fair)	23% LVEF, 70% HF due to IHD, 84% NYHA class III, 16% class IV	Number screened not reported/number eligible not reported/166 enrolled	Number withdrawn not reported (stated that 156 completed trial per protocol)/number lost to fu not reported/166 analyzed

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Results	Results
Lang, 1997 U.S., Canada (Fair)	**Endpoints:** symptom-limited treadmill exercise duration: mean change (sd) in seconds Losartan 25 = 37 (135) Losartan 50 = 37 (119) Enalapril = 49 (123) 6-min walk test: mean change (sd) in m Losartan 25 = 9 (48) Losartan 50 = 3 (71) Enalapril = 0 (63) dyspnea-fatigue index: mean change (sd) Losartan 25 = 0.4 (1.5) Losartan 50 = 0.3 (1.7) Enalapril = 0.5 (1.7)	**Endpoints:** signs and symptoms of HF: no statistically significant difference among treatment groups NYHA functional class: # (%) improvement Losartan 25 = 6 (15.7%) Losartan 50 = 6 (15.7%) Enalapril = 7 (18.4%)
Dickstein, 1995 Scandinavia (Fair)	**Primary endpoints (exercise capacity):** 6-min walk test: mean (sd) change at 8 weeks in m Losartan 25 mg = 18 (60) Losartan 50 mg = 12 (50) Enalapril 20 mg = 14 (48) dyspnea-fatigue index: mean (sd) change at 8 weeks Losartan 25 mg = 0.7 (2.0) Losartan 50 mg = 0.4 (1.7) Enalapril 20 mg = 0.7 (1.7)	**Primary endpoints:** clinical status: No statistically significant differences among treatments were observed NYHA functional class: % worsening class: Losartan 25 mg = 1.9% Losartan 50 mg = 5.3% Enalapril 20 mg = 1.7%

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Lang, 1997 U.S., Canada (Fair)	Not reported	Potassium: losartan 25mg -0.16+0.43 mEq/L vs. losartan 50mg 0.12+0.42 mEq/L vs. enalapril -0.05+0.47 mEq/L; sCr: losartan 25mg 0.02+0.14 mg/dl vs. losartan 50mg 0.02+0.28 mg/dl vs. enalapril 0.08+0.15 mg/dl (losartan 50mg vs. enalapril P<0.05)	Total withdrawals not reported/3 withdrawals due to adverse clinical experiences (1 in each group)
Dickstein, 1995 Scandinavia (Fair)	Not reported	Dizziness: losartan 25mg (9.6%) vs. losartan 50mg (8.9%) vs. enalapril 20mg (6.9%); hypotension: losartan 25mg (5.8%) vs. losartan 50mg (7.1%) vs. enalapril 20mg (6.9%); cough: losartan 25mg (3.8%) vs. losartan 50mg (7.1%) vs. enalapril 20mg (6.9%)	Total withdrawals not reported/losartan 25mg 1.9% vs. losartan 50mg 3.6% vs. enalapril 20mg 8.6% discontinued treatment due to adverse experience

Evidence Table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author Year Country Trial Name (Quality Score)	Comments
Lang, 1997 U.S., Canada (Fair)	5 deaths occurred in the losartan 50mg group compared to 1 in the losartan 25mg group and none in the enalapril group (none of the deaths were considered to be related to study drug)
Dickstein, 1995 Scandinavia (Fair)	Pilot trial. 89% patients on maintenance ACEI prior to enrollment

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout Period
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	RCT, combined results of 3 component trials, multicenter	Men and women ≥ 18 years of age, symptomatic HF (NYHA class II-IV) for ≥ 4 weeks	Candesartan 4mg or 8mg (decided by study physician), doubled minimum every 2 weeks (as tolerated) to target dose 32mg once daily Median follow-up 3.1 years	None
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	RCT, multicenter	Men and women ≥ 18 years of age, symptomatic HF (NYHA class II-IV; if class II, required cardiac hospitalization within previous 6 months), LVEF ≤ 40% measured within the past 6 months, treatment with the same dose of an ACEI for ≥ 30 days	Candesartan 4mg or 8mg (decided by study physician), doubled minimum every 2 weeks (as tolerated) to target dose 32mg once daily Median follow-up 3.4 years	None

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	Standard therapy for HF; Baseline: ACEIs, if appropriate per protocol (41%), beta-blocker (55%), diuretic (83%), digoxin (43%), spironolactone (17%), CCB (20%), other vasodilators (38%), aspirin (55%)	Primary endpoint was all-cause death. All deaths classified as CV unless non-CV cause established. Clinic visits every 4 months; laboratory assessments in North America at baseline, 6 weeks, 14 months, then every year.	Mean age 66 68% male, 90% European, 4% black, 6% other
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	ACEI, standard therapy for HF; Baseline: ACEI (100%), beta-blocker (55%), diuretic (90%), digoxin (58%), spironolactone (17%), other vasodilators (37%), aspirin (51%)	Primary endpoint was CV death or unplanned admission for worsening CHF (signs and symptoms of worsening CHF requiring IV diuretics). Secondary outcomes included: CV death, CHF admission, or non-fatal MI (diagnosis made by cardiac markers and ECG changes or clinical presentation); CV death, CHF admission, non-fatal MI, or non-fatal stroke; CV death, CHF admission, non-fatal MI, non-fatal stroke, or coronary revascularization; any death or CHF admission; new-onset DM Clinic visit at 2, 4, and 6 weeks, at 6 months, then every 4 months; laboratory assessments in North America at baseline, 6 weeks, then every year.	Mean age 64 79% male, 90% European, 5% black, 5% other

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	LVEF < 30% (28%), ≥ 30-39% (29%), > 40-49% (18%), ≥ 50% (17%); 45% NYHA class II, 52% class III, 3% class IV; MI 53%, stroke 9%, HTN 55%, DM 28%	Number screened not reported/7601 eligible/7599 enrolled	1189 discontinued study medication/10 lost to fu/7599 analyzed
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	28% LVEF; 24% NYHA class II, 73% class III, 3% class IV; 62% IHD as cause of HF; MI 56%, stroke 9%, HTN 48%, DM 30%	Number screened not reported/number eligible not reported/2548 enrolled	375 discontinued study medication/4 lost to fu/2548 analyzed

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Results
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	**Primary endpoint (all-cause mortality):** candesartan vs. placebo: unadjusted HR 0.91 (95% CI 0.83-1.00; P=0.055)	**Secondary endpoints:** candesartan vs. placebo: combined CV death or HF hospitalization HR 0.84 (95% CI 0.77-0.91, P<0.0001); CV death HR 0.88 (95% CI 0.79-0.97, P=0.012); HF hospitalizations HR 0.79 (95% CI 0.72-0.87, P<0.0001)
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	**Primary endpoint (CV death or HF hospitalization):** candesartan vs. placebo: HR 0.85 (95% CI 0.75-0.96; P=0.011) calculated NNT=23 (95% CI 12-156)	**Secondary endpoints:** candesartan vs. placebo: combined CV death, HF hospitalization, MI HR 0.85 (95% CI 0.76-0.96, P=0.010); combined CV death, HF hospitalization, MI, stroke HR 0.87 (95% CI 0.77-0.98, P=0.020); combined CV death, HF hospitalization, MI, stroke, coronary revascularization procedure HR 0.87 (95% CI 0.77-0.97, P=0.015); all-cause mortality HR 0.89 (95% CI 0.77-1.02, P=0.086); CV death HR 0.84 (95% CI 0.72-0.98, P=0.029); HF hospitalizations HR 0.83 (95% CI 0.71-0.96, P=0.014)

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	candesartan vs. placebo: combined CV death, HF hospitalization, MI HR 0.84 (95% CI 0.78-0.91, P<0.0001); combined CV death, HF hospitalization, MI, stroke HR 0.85 (95% CI 0.79-0.92, P<0.0001); combined CV death, HF hospitalization, MI, stroke, coronary revascularization procedure HR 0.86 (95% CI 0.80-0.93, P<0.0001)	Not reported	Adverse events leading to discontinuation: hypotension: candesartan 3.5% vs. placebo 1.7% (P<0.0001); increased sCr: candesartan 6.2% vs. placebo 3.9% (P<0.0001); hyperkalemia: candesartan 2.2% vs. placebo 0.6% (P<0.0001)
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	Subgroup analyses +ACEI/+BB (n=497), +ACEI/-BB (n=524) candesartan vs. placebo: all-cause mortality +ACEI/+BB HR 0.88 (95% CI 0.72-1.08, P=0.22), +ACEI/-BB RR 0.88 (95% CI 0.73-1.07, P=0.20)	Not reported	Adverse events leading to discontinuation: hypotension: candesartan 4.5% vs. placebo 3.1% (P=0.79); increased sCr: candesartan 7.8% vs. placebo 4.1% (P=0.0001); hyperkalemia: candesartan 3.4% vs. placebo 0.7% (P<0.0001)

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	Angioedema: candesartan 5/3803 (0.13%) vs. placebo 3/3796 (0.08%); of 2743 with lab surveillance, sCr doubled in candesartan 82/1263 (6%) vs. placebo 47/1279 (4%) (P=0.002); serum potassium increased 0.14 mmol/L with candesartan (P<0.0001) with no change in the placebo group at 6 weeks; potassium $\geq$ 6.0 mmol/L was seen in 31/1294 (2%) of candesartan vs. 15/1310 (1%) placebo (P=0.017)	1189 of the survivors discontinued study medication/1430 withdrew due to adverse events or lab abnormalities (797/3803 candesartan 21.0% vs. 633/3796 placebo 16.7%; P<0.0001)
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	Angioedema: candesartan 2/1276 (0.16%) vs. placebo 3/1272 (0.24%) (all were on ACEIs); in those with lab surveillance, sCr at least doubled with candesartan 32/436 (7%) vs. placebo 27/447 (6%) (P=0.5); potassium $\geq$ 6.0 mmol/L was seen in 12/447 (3%) of candesartan vs. 5/459 (1%) placebo (P=0.089)	375 of the survivors discontinued study medication/542 withdrew due to adverse events or lab abnormalities (309/1276 candesartan 24.2% vs. 233/1272 placebo 18.3%; P=0.0003)

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Comments
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	Overall results of the 3 trials combined showed a reduction in mortality with candesartan in patients with HF (borderline significance), primarily due to lower rates of CV death with candesartan. The benefit with candesartan was seen regardless of baseline treatment with ACEIs, beta-blockers, or other HF medication classes. Annual mortality rates were 8.1% on candesartan and 8.8% on placebo. At 6 months, target dose achieved in 63% (mean 24mg) on candesartan and 75% on placebo. At 6 months, SBP decreased 5.2 mm Hg and DBP 3.0 mm Hg from baseline on candesartan (P<0.001 vs. placebo).
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	The addition of an AIIRA to an ACEI reduced CV death and HF hospitalization compared to treatment with an ACEI. Benefit was seen regardless of baseline treatment with beta-blockers, or other HF medication classes. Investigators felt 96% patients on optimal ACEI doses (enalapril 16.8 and 17.2mg/d , lisinopril 17.7 and 17.7mg/d, captopril 82.2 and 82.7mg/d, ramipril 6.8 and 7.3mg/d in the candesartan and placebo groups, respectively). At 6 months, target dose achieved in 61% (mean 24mg) on candesartan and 73% on placebo. At 6 months, SBP decreased 4.6 mm Hg (P=0.007) and DBP 3.0 mm Hg (P=0.004) from baseline on candesartan vs. placebo.

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout Period
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	RCT, multicenter	Men and women ≥ 18 years of age, symptomatic HF (NYHA class II-IV) for ≥ 4 weeks, LVEF < 40%, ACEI intolerance	Candesartan 4mg or 8mg (decided by study physician), doubled minimum every 2 weeks (as tolerated) to target dose 32mg once daily Median follow-up 2.8 years	None
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	RCT, multicenter	Men and women ≥ 18 years of age, symptomatic HF (NYHA class II-IV) for ≥ 4 weeks, history cardiac hospitalization, LVEF > 40%	Candesartan 4mg or 8mg (decided by study physician), doubled minimum every 2 weeks (as tolerated) to target dose 32mg once daily Median follow-up 3.1 years	None

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	Standard therapy for HF (although intolerant of ACEI); Baseline: beta-blocker (55%), diuretic (85%), digoxin (45%), spironolactone (24%), other vasodilators (42%), aspirin (57%)	Primary endpoint was CV death or unplanned admission for worsening CHF (signs and symptoms of worsening CHF requiring IV diuretics). Secondary outcomes included: CV death, CHF admission, or non-fatal MI (diagnosis made by cardiac markers and ECG changes or clinical presentation); CV death, CHF admission, non-fatal MI, or non-fatal stroke; CV death, CHF admission, non-fatal MI, non-fatal stroke, or coronary revascularization; any death or CHF admission; new-onset DM Clinic visit at 2, 4, and 6 weeks, at 6 months, then every 4 months; laboratory assessments in North America at baseline, 6 weeks, and 14, 26, and 38 months.	Mean age 66 68% male, 88% European, 4% black, 8% other
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	Baseline: ACEI (19%), beta-blocker (56%), diuretic (75%), digoxin (28%), spironolactone (11%), CCB (31%), other vasodilators (38%), aspirin (58%)	Primary endpoint was CV death or unplanned admission for worsening CHF (signs and symptoms of worsening CHF requiring IV diuretics). Secondary outcomes included: CV death, CHF admission, or non-fatal MI (diagnosis made by cardiac markers and ECG changes or clinical presentation); CV death, CHF admission, non-fatal MI, or non-fatal stroke; CV death, CHF admission, non-fatal MI, non-fatal stroke, or coronary revascularization; any death or CHF admission; new-onset DM Clinic visit at 2, 4, and 6 weeks, at 6 months, then every 4 months; laboratory assessments in North America at baseline, 6 weeks, then yearly. Adjudicated outcomes by blinded committee for cause of death, first MI, and first CHF admission were basis for formal analysis; investigator reported events were also analyzed.	Mean age 67 60% male, 92% European, 4% black, 4% other

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	30% LVEF; 48% NYHA class II, 48% class III, 4% class IV; 69% IHD as cause of HF; MI 61%, stroke 9%, HTN 49%, DM 27%	Number screened not reported/number eligible not reported/2028 enrolled	338 discontinued study medication/3 lost to fu/2028 analyzed
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	54% LVEF; 61% NYHA class II, 37% class III, 2% class IV; 56% IHD as cause of HF; MI 45%, stroke 9%, HTN 65%, DM 28%	Number screened not reported/3025 eligible/3023 enrolled	488 discontinued study medication/3 lost to fu/3023 analyzed

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Results
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	**Primary endpoint (CV death or HF hospitalization):** candesartan vs. placebo: HR 0.77 (95% CI 0.67-0.89; P=0.0004) calculated NNT=14 (95% CI 9-35)	**Secondary endpoints:** candesartan vs. placebo: combined CV death, HF hospitalization, MI HR 0.78 (95% CI 0.68-0.90, P=0.0007); combined CV death, HF hospitalization, MI, stroke HR 0.80 (95% CI 0.69-0.91, P=0.001); combined CV death, HF hospitalization, MI, stroke, coronary revascularization procedure HR 0.81 (95% CI 0.71-0.92, P=0.002)
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	**Primary endpoint (CV death or HF hospitalization):** candesartan vs. placebo: HR 0.89 (95% CI 0.77-1.03; P=0.118)	**Secondary endpoints:** candesartan vs. placebo: combined CV death, HF hospitalization, MI HR 0.90 (95% CI 0.78-1.03, P=0.126); combined CV death, HF hospitalization, MI, stroke HR 0.88 (95% CI 0.77-1.01, P=0.078); combined CV death, HF hospitalization, MI, stroke, coronary revascularization procedure HR 0.91 (95% CI 0.80-1.03, P=0.123)

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	candesartan vs. placebo: all-cause mortality HR 0.87 (95% CI 0.74-1.03, P=0.11); CV death HR 0.85 (95% CI 0.71-1.02, P=0.072); HF hospitalizations HR 0.68 (95% CI 0.57-0.816, P<0.0001)	Not reported	Adverse events leading to discontinuation: hypotension: candesartan 3.7% vs. placebo 0.9% (P<0.0001); increased sCr: candesartan 6.1% vs. placebo 2.7% (P<0.0001); hyperkalemia: candesartan 1.9% vs. placebo 0.3% (P=0.0005); cough: candesartan 0.2% vs. placebo 0.4% (P=0.69); angioedema: candesartan 0.1% vs. placebo 0.0% (P=0.50)
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	candesartan vs. placebo: CV death HR 0.99 (95% CI 0.80-1.22, P=0.918); HF hospitalizations HR 0.85 (95% CI 0.72-1.01, P=0.072)	Not reported	Adverse events leading to discontinuation: hypotension: candesartan 2.4% vs. placebo 1.1% (P=0.009); increased sCr: candesartan 4.8% vs. placebo 2.4% (P=0.0005); hyperkalemia: candesartan 1.5% vs. placebo 0.6% (P=0.029)

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	Angioedema: candesartan 3/1013 (0.30%) vs. placebo 0/1015 (0.0%), all cases of angioedema were in patients with previous ACEI intolerance due to angioedema or anaphylaxis; of patients with lab surveillance, sCr at least doubled in 5.5% of 311on candesartan vs. 1.6% of 307 on placebo (P=0.015); potassium $\geq$ 6.0 mmol/L was seen in 3% of 321 on candesartan (n=321) vs. 1.3% of 315 on placebo (P=0.26)	338 of the survivors discontinued study medication/414 withdrew due to adverse events or lab abnormalities (218/1013 candesartan 21.5% vs. 196/1015 placebo 19.3%; P=0.23)
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	Of patients with lab surveillance, sCr at least doubled in 6% on candesartan vs. 3% on placebo (P=0.007); potassium $\geq$ 6.0 mmol/L was seen in 2% on candesartan vs. 1% on placebo (P=0.32)	488 of the survivors discontinued study medication/474 withdrew due to adverse events or lab abnormalities (270/1514 candesartan 17.8% vs. 204/1509 placebo 13.5%; P=0.001)

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Comments
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	Use of an AIIRA in patients unable to tolerate an ACEI reduced CV death and HF hospitalization compared to placebo. At 6 months, target dose achieved in 59% (mean 23mg) on candesartan and 73% on placebo. At 6 months, SBP decreased 4.4 mm Hg and DBP 3.9 mm Hg from baseline on candesartan vs. placebo (P<0.0001 for both)
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	Use of an AIIRA in patients with HF and preserved LVEF did not differ significantly from that of placebo. At 6 months, target dose achieved in 67% (mean 25mg) on candesartan and 79% on placebo. At 6 months, SBP decreased 6.9 mm Hg and DBP 2.9 mm Hg from baseline on candesartan vs. placebo (P<0.0001)

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout Period
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	RCT, multicenter	Men and women ≥ 18 years of age, clinical findings of HF for at least 3 months before screening, NYHA class II, III, or IV and clinically stable, LVEF < 40% and LV dilatation on ECHO, and at least 2 weeks on fixed-dose regimen that could include an ACEI, diuretic, digoxin, and beta-blocker	Valsartan 40mg twice daily, doubled every 2 weeks to 160mg twice daily Mean follow-up 1.9 years	Single-blind twice daily placebo run-in of 2 to 4 weeks to confirm eligibility, clinical stability, assess adherence
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis (Fair)	RCT, multicenter	Men and women ≥ 18 years of age, clinical findings of HF for at least 3 months before screening, NYHA class II, III, or IV and clinically stable, LVEF < 40% and LV dilatation on ECHO, and at least 2 weeks on fixed-dose regimen that could include an ACEI, diuretic, digoxin, and beta-blocker; subgroup analysis was in patients who were not treated with an ACEI	Valsartan 40mg twice daily, doubled every 2 weeks to 160mg twice daily Mean follow-up 1.9 years	Single-blind twice daily placebo run-in of 2 to 4 weeks to confirm eligibility, clinical stability, assess adherence
Tonkon, 2000 U.S. (Poor)	RCT, multicenter	Men and postmenopausal or surgically sterile women ≥ 18 years of age with stable HF NYHA class II or III, LVEF ≤ 40%, and ≥ 6 weeks on stable doses of an ACEI and ≥ 2 weeks on a diuretic, seated SBP ≥ 90 mm Hg, sCr ≤ 2.2 mg/dl, BUN ≤ 50 mg/dl	Irbesartan starting doses of 12.5mg, 37.5mg, or 75mg, titrated at weekly intervals to target dose 150mg once daily for as maximum of 4 weeks; open-label ACEI determined by investigator and maintained at constant dose Mean follow-up 12 weeks	AIIRAs, beta-blockers, CCBs, vasodilators, NSAIDs were withdrawn and ACEI and diuretics were stabilized

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	Standard therapy for HF; Baseline:ACEIs (93%), beta-blocker (35%), diuretic (85%), digoxin (67%)	Two primary endpoints: mortality and combined mortality and morbidity (defined as cardiac arrest with resuscitation, hospitalization for HF, or IV inotropes or vasodilators for > 4 hours without hospitalization); secondary endpoints included change from baseline to last available observation of LVEF, NYHA class, QOL, signs and symptoms of HF. Patient evaluation at 2, 4, and 6 months and then every 3 months; 60% of patients received a QOL assessment using the Minnesota Living with HF questionnaire	Mean age 63 80% male, 90% white, 7% black, 3% other
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis (Fair)	Standard therapy for HF except for 7.3% of 5010 in Val-HeFT that did not receive ACEIs Baseline: beta-blocker (38%), diuretic (80%), digoxin (59%), spironolactone (7%)	Two primary endpoints: mortality and combined mortality and morbidity (defined as cardiac arrest with resuscitation, hospitalization for HF, or IV inotropes or vasodilators for > 4 hours without hospitalization); secondary endpoint included QOL (assessed using the Minnesota Living with HF Questionnaire MLWHFQ); subanalysis of exercise capacity after 4 months by 6-min walk test. Patient evaluation at 2, 4, and 6 months and then every 3 months	Mean age 67 76% male, 82% white, 12% black
Tonkon, 2000 U.S. (Poor)	Digoxin and long-acting nitrates (in addition to ACEI and diuretics)	Main endpoints include exercise tolerance (assessed by symptom-limited maximum exercise treadmill test) and clinical status (NYHA functional class determination) performed at 24±3hrs after administration of baseline study medication and at 6, 8, and 12 weeks	Mean age 64 71% male, 95% white

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	27% LVEF, 57% CHD as cause of HF, 62% NYHA class II and 36% class III	Number screened not reported/number eligible not reported/5010 enrolled	430 withdrawn due to adverse events/number lost to fu not reported/5010 analyzed
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis (Fair)	28% LVEF, 68% CHD as cause of HF, 47% NYHA class III-IV	Number screened not reported/number eligible not reported/5010 enrolled in Val-HeFT/366 not treated with ACEI in substudy	77 withdrawn/number lost to fu not reported/366 analyzed
Tonkon, 2000 U.S. (Poor)	28% LVEF, 53% IHD as cause of HF, 79% NYHA class II, 21% class III	Number screened not reported/145 enrolled/109 randomized	12 withdrawn/number lost to fu not reported/97 analyzed

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Results
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	**Primary endpoints (mortality and combined mortality and morbidity):** valsartan vs. placebo: all-cause mortality RR 1.02 (98% CI 0.88-1.18; P=0.80); combined morbidity and mortality RR 0.87 (97.5% CI 0.77-0.97; P=0.009), calculated NNT=31 (95% CI 17-140)	**Secondary endpoints:** valsartan vs. placebo: HF hospitalizations RR 0.725 (P<0.001); mean change in LVEF (4% vs. 3.2%, P=0.001); improvement in NYHA class (23.1% vs. 20.7%), worsening (10.1% vs. 12.8%) (P<0.001); signs and symptoms of HF improved with valsartan vs. placebo (P<0.01); QOL (little change with valsartan vs. worsening average 1.9 with placebo, P=0.005)
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis (Fair)	**Primary endpoints:** mortality: number (%) Valsartan = 32 (17.3%) Placebo = 49 (27.1%) RR = 0.67 95% CI (0.42-1.06) combined mortality and morbidity: number (%) Valsartan = 46 (24.9%) Placebo = 77 (42.5%) RR = 0.56 95% CI (0.39-0.81) NNT = 6 (95% CI 4-12)	**Secondary endpoints:** HF hospitalizations:number (%) Valsartan = 24 (13.0%) Placebo = 48 (26.5%) CV death:number (%) Valsartan = 29 (15.7%) Placebo = 40 (22.1%) QOL:mean change (sem) Valsartan = -0.98 (1.71) Placebo = 3.17 (1.98)
Tonkon, 2000 U.S. (Poor)	**Main endpoint (exercise tolerance):** exercise treadmill test: median change from baseline at week 12 irbesartan: +64 seconds (IQR +21 TO +109) placebo: +41 seconds (IQR: -19 to +131)	**Main endpoint (clinical status):** NYHA functional class: of patients who changed classes irbesartan: 14% improved, 7% worsened placebo: 14% improved, 12% worsened

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	Subgroup analyses: [+ACEI/-BB (n=3034); +ACEI/+BB (n=1610); -ACEI/-BB (n=226); -ACEI/+BB (n=140)] valsartan vs. placebo: mortality +ACEI/+BB RR > 1.0 (P=0.009), -ACEI/-BB RR < 1.0 (P=0.012), -ACEI/+BB RR 0.67 (95% CI 0.42-1.06); combined morbidity and mortality +ACEI/+BB RR > 1.0 (P=0.10), -ACEI/-BB (P=0.003), +ACEI/-BB (P=0.002), -ACEI/+BB (P=0.037), -ACEI/±BB RR 0.56 (95% CI 0.39-0.81); combined morbidity and mortality in black patients (n=344) RR 1.11 (95% CI 0.77-1.61)	Not reported	Adverse events leading to discontinuation: dizziness: valsartan 1.6% vs. placebo 0.4% (P<0.001); hypotension: valsartan 1.3% vs. placebo 0.8% (P=0.124); renal impairment: valsartan 1.1% vs. placebo 0.2% (P<0.001)
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis (Fair)	Exercise capacity substudy:for the 35 patients in the substudy mean change in walk distance: Valsartan = 50.3 m Placebo = -34.2 m P = 0.022	Not reported	Adverse events leading to discontinuation: hypotension: valsartan 0.5% vs. placebo 0.6% (P=0.988); life-threatening laboratory abnormalities: valsartan 0.5% vs. placebo 0.6% (P=0.988)
Tonkon, 2000 U.S. (Poor)		Spontaneously reported adverse events and adverse events elicited by general questioning were recorded	Adverse events leading to discontinuation: cardiovascular events: irbesartan 4 vs. placebo 2

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	Mean change BUN: valsartan increase 5.9mg/dl vs. placebo increase 3.3mg/dl (P<0.001); mean change sCr: valsartan increase 0.18mg/dl vs. placebo increase 0.10mg/dl (P<0.001); mean change serum potassium: valsartan increase 0.12mmo/l vs. placebo decrease 0.07mmol/l (P<0.001)	Overall adverse events leading to discontinuation: valsartan 249 (9.9%) vs. placebo 181 (7.2%) (P<0.001)
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis (Fair)	Dizziness: valsartan 23.9% vs. placebo 18.9%; hypotension: valsartan 14.7% vs. placebo 5.6%; increase sCr: valsartan 0.18+0.2mg/dl vs. placebo 0.10+0.02mg/dl (P=0.009)	77 total withdrawals (17.3% valsartan vs. 24.9% placebo)/41 withdrawals due to adverse events (18/185 valsartan 9.7% vs. 23/181 placebo 12.7%; P=0.367)
Tonkon, 2000 U.S. (Poor)	Dizziness: irbesartan 23% vs. placebo 23%; hypotension: irbesartan 12% vs. placebo 0%; headache: 19% vs. placebo 12%; potassium: irbesartan 0.01 mEq/L vs. placebo -0.08mEq/L; sCr: irbesartan 0.08 mg/dl vs. placebo 0.04 mg/dl	12 total withdrawals (7 irbesartan; 5 placebo)/6 withdrawals due to adverse events (4 irbesartan; 2 placebo)

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Comments
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	Results showed that valsartan added to standard therapy for HF did not improve survival but did have a benefit in decreasing the combined morbidity and mortality endpoint. Subgroup analyses showed higher mortality in patients on valsartan in combination with an ACEI and beta-blocker. A decrease in mortality as well as the combined endpoint was seen in patients on valsartan ± beta-blocker but -ACEI. Treatment with valsartan + ACEI decreased the combined endpoint compared to an ACEI alone. Patients were randomized according to baseline beta-blocker but not ACEI use. Annual mortality on placebo 9% (12% anticipated). Target dose achieved in 84% (mean 254mg) on valsartan and 93% on placebo. SBP decreased 5.2±16 mm Hg on valsartan vs. 1.3±15.0 mm Hg on placebo at 1 year.
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis (Fair)	Higher percentage of patients in NYHA class III-IV compared to patients on ACEI in Val-HeFT (P<0.05). SBP decreased 8.1±1.2 mm Hg on valsartan vs. 3.2±1.2 mm Hg on placebo at last observation (P=0.004)
Tonkon, 2000 U.S. (Poor)	Not powered to demonstrate statistically significant benefit for any endpoint

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout Period
Riegger, 1999 Europe STRETCH Trial (Fair)	RCT, multicenter	Men and women 21 to 80 years of age with mild to moderate symptomatic HF (NYHA class II or III), LVEF 30 to 45%	Candesartan 4mg, 8mg, 16mg or placebo for 12 weeks (titrated to 8mg and 16mg doses at weekly intervals)	4 week placebo run-in, stabilized on diuretics, cardiac glycosides, long-acting nitrates; 2 week washout for patients on ACEI
Hamroff, 1999 U.S., France (Fair)	RCT, multicenter	Patients with symptomatic HF consistent with NYHA class III or IV	Losartan 50mg once daily vs. placebo for 6 months	2 week single-blind tolerability phase

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	
Riegger, 1999 Europe STRETCH Trial (Fair)	Diuretics, cardiac glycosides, long-acting nitrates kept constant	Primary endpoint was total exercise time determined by bicycle ergometry $\geq$ 2 times during run-in and at 6 and 12 weeks during treatment. Secondary endpoints included signs and symptoms of HF and NYHA functional class	Mean age 62 male, 99.8% white	68%
Hamroff, 1999 U.S., France (Fair)	Treatment with maximally tolerated doses of ACEI > 3 months, in addition to digoxin and diuretics; other therapy for HF allowed including beta-blockers	Primary endpoint included NYHA functional class assessed prior to randomization and at 3 and 6 months. Secondary endpoints included laboratory safety parameters and doses of concomitant background medications.	Mean age 61 male, ethnicity not specified	49%

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Riegger, 1999 Europe STRETCH Trial (Fair)	39% LVEF, 71% CHD as cause of HF, 81% NYHA class II, 19% class III	Number screened not reported/926 enrolled/844 randomized	55 withdrawn/number lost to fu not reported/807 analyzed ITT; 629 per-protocol population
Hamroff, 1999 U.S., France (Fair)	26% LVEF, 30% IHD as cause of HF, NYHA class 3.2	Number screened not reported/number eligible not reported/33 enrolled	7 withdrawn/2 lost to fu/33 analyzed

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Results
Riegger, 1999 Europe STRETCH Trial (Fair)	**Primary endpoint (total exercise time):** bicycle ergometry: mean change from baseline for <=12 weeks placebo 30.8 seconds; Candesartan 4mg 39.7 seconds; Candesartan 8 mg 45.8 seconds (approached being significantly different from placebo P=0.069); Candesartan 16 mg 47.2 seconds (significantly different from placebo P=0.046)	**Secondary endpoints:** signs and symptoms of HF: NYHA functional class % of patients with change in NYHA functional class Placebo 13.9% improved, 84.6% no change, 1.5% deteriorated; Candesartan 4mg 19.2% improved, 79.8% no change, 1.0% deteriorated; Candesartan 8 mg 20.3% improved, 79.7% no change, 0% deteriorated; Candesartan 16 mg 16.9% improved, 82.1% no change, 1.0% deteriorated. None of the Candesartan groups were significantly different from placebo
Hamroff, 1999 U.S., France (Fair)	**Primary endpoints:** NYHA functional class % improvemed by at least 1 NYHA class losartan: 56% vs placebo: 6% NNT = 2 (95% CI 1-4) Mean (sem) functional class at baseline, 3 months, 6 months losartan: 3.2(0.4), 2.9 (0.6), 2.5(0.5) placebo: 3.0(0.4), 3.0 (0.5), 3.0(0.5)	**Secondary endpoints:** Doses of concomitant background medications: mean(sem) furosemide dose in mg at baseline, 3 months, 6 months losartan: 11.5(1.1), 10.9(1.1), 10.5(1.2) placebo: 9.9(1.0), 10.0(1.1), 10.8(1.1) Laboratory parameters: Serum electrolytes, creatinine, and blood urea nitrogen were unchanged in both groups Doses of other background medications were unchanged in both treatment groups

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Riegger, 1999 Europe STRETCH Trial (Fair)		All adverse events recorded and intensity rated as mild, moderate, or severe	Serious adverse events: candesartan 4mg (1.4%) vs. candesartan 8mg (5.7%) vs. candesartan 16mg (5.6%) vs. placebo (4.7%)
Hamroff, 1999 U.S., France (Fair)		Not reported	Adverse events leading to discontinuation: nausea in 1 patient on losartan, nausea in 1 patient on placebo

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Riegger, 1999 Europe STRETCH Trial (Fair)	Adverse events possibly related to symptomatic hypotension: candesartan 4mg (1.5%) vs. candesartan 8mg (2.8%) vs. candesartan 16mg (0.5%) vs. placebo (1.9%); increase in sCr: candesartan 4mg (2.9%) vs. candesartan 8mg (4.2%) vs. candesartan 16mg (0.9%) vs. placebo (1.9%)	55 total withdrawals (7 candesartan 4mg; 12-19 per other treatment groups)/35 withdrawals due to adverse events: candesartan 4mg (1.9%) vs. candesartan 8mg (4.7%) vs. candesartan 16mg (5.6%) vs. placebo (4.3%)
Hamroff, 1999 U.S., France (Fair)	Treatment reported to be well-tolerated in both groups, without adverse side effects	7 total withdrawals (3 losartan; 4 placebo)/2 withdrawals due to adverse events (1 in each group)

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Comments
Riegger, 1999 Europe STRETCH Trial (Fair)	Phase 2 trial
Hamroff, 1999 U.S., France (Fair)	Mean daily dose of captopril 175mg in the losartan group vs. 117mg in the placebo group, method of adjustment of concomitant medications (secondary endpoint) not described

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout Period
Warner, 1999 U.S. (Fair)	RCT with crossover	Patients evaluated for CAD as cause of dyspnea with LVEF > 50%, SBP $\leq$ 150 mm Hg, mitral valve Doppler flow pattern with peak E wave less than peak A wave velocity (E/A < 1.0), and hypertensive response to exercise with peak SBP > 200 mm Hg, no previous AIIRA use	Losartan 50mg once daily vs. placebo for 2 weeks, wash-out for 2 weeks, then crossed over to losartan or placebo for 2 weeks	2 week washout in between two, 2 week treatments

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Warner, 1999 U.S. (Fair)	All baseline medications continued during study (7/20 beta-blocker, 6/20 diuretic, 5/20 CCB, 6/20 ACEI)	Main endpoints include exercise tolerance (assessed by treadmill exercise test using modified Bruce Protocol) and QOL (Minnesota Living With Heart Failure questionnaire) at baseline and after 2 weeks of treatment, 2 to 4 hrs after study medication; tests were then repeated after 2 weeks of being crossed over to the other treatment	Mean age 64 20% male, ethnicity not specified

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Warner, 1999 U.S. (Fair)	80% HTN, resting BP 143/79±8.8 mm Hg	Number screened not reported/number eligible not reported/21 enrolled	1 withdrawn/none lost to fu/20 analyzed

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Results
Warner, 1999 U.S. (Fair)	**Main endpoint (exercise tolerance): note: crossover study** treadmill exercise test: mean (sd) exercise time Baseline: 11.3(2.5) min Placebo: 11.0(2.0) min Losartan: 12.3(2.6) min Losartan significantly different from both placebo and baseline (P<0.05)	**Main endpoint (QOL):** Minnesota Living With Heart Failure questionnaire: mean (sd) score Baseline: 25(22) Placebo: 22(26) Losartan: 18(22) Losartan significantly different from placebo (P<0.05)

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Warner, 1999 U.S. (Fair)		Not reported	1 patient on losartan withdrew due to increase in sCr from 1.5 to 2.0mg/dl

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Warner, 1999 U.S. (Fair)		1 total withdrawal (losartan)/1 withdrawal due to adverse event (losartan)

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Comments
Warner, 1999 U.S. (Fair)	

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout Period
Granger, 2000 U.S., Canada, Europe (Fair)	Multicenter	Left ventricular ejection fraction less than 35%; CHF (NYHA class II through IV); intolerance of ACE inhibitors (perceived angioedema, anaphylaxis, neutropenia, cough, symptomatic hypotension or azotemia)	Candesartan 4-16 mg once daily Placebo Titration at 2 weeks (8 mg) and 4 weeks (16 mg) Duration 12 weeks	1-week single-blind placebo run-in

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Granger, 2000 U.S., Canada, Europe (Fair)	Not reported	Evaluations or quality of life (Minnesota Living with Heart Failure questionnaire and SF-36 Health Survey) and adverse events conducted after 2, 4, 6, 8 and 12 weeks	65.7 68.9% male Ethnicity not reported

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Granger, 2000 U.S., Canada, Europe (Fair)	NYHA class II=53.7% NYHA class III=40.7% NYHA class IV=5.5% Ischemic cause of heart failure=71.5% Medical history MI=62.2% Stroke=6.3% Hypertension=37.4% Diabetes=18.9% Atrial fibrillation or flutter=24.4% Sustained ventricular tachycardia or fibrillation=12.2% Implanted defibrillator=2.9% Medications Digoxin=61.1% Diuretics=74.4% Beta Blockers=21.1% ARBs(> 1 month pre-randomization)=10.4% Aspirin=55.9% Hydralazine=12.6% Lipid-lowering agents=24.8% Amiodarone=15.2%	Number screened not reported/288 eligible/270 enrolled	43(15.9%) withdrawn/0 lost to fu/270 analyzed

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Results
Granger, 2000 U.S., Canada, Europe (Fair)	Minnesota Living with Heart Failure Questionnaire (% change): Candesartan=0 Placebo=9.5% decline median scores at baseline and final visit Candesartan: 32, 32 SF-36 *Better* Candesartan=45% Placebo=54% *Worse* Candesartan=11% Placebo=9%	

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Granger, 2000 U.S., Canada, Europe (Fair)		Not reported	Cough Placebo=64.8% Candesartan=68.2% Renal Failure Placebo=11.0% Candesartan=11.2% Angioedema Placebo=4.4% Candesartan=4.5% Mortality Placebo=3.3% Candesartan=3.4

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Granger, 2000 U.S., Canada, Europe (Fair)		43 total withdrawals (31/179 candesartan 17.3% vs. 12/91 placebo 13.2%)/29 withdrawals due to adverse events (21/179 candesartan 11.7% vs. 8/91 placebo 8.8%) Discontinuation because of renal insufficiency Placebo=3% Candesartan=7%

Evidence Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author Year Country Trial Name (Quality Score)	Comments
Granger, 2000 U.S., Canada, Europe (Fair)	

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Study Design (optional) Setting	Eligibility criteria	Interventions (drug, dose, duration)
Nakao, 2003 Japan COOPERATE (Good)	RCT, AIIRA vs. ACEI vs. combination	Age between 18 and 70 years, chronic nephropathy (defined as sCr 133-398umol/L or GFR 20-70 ml/min/1.73m2), non-diabetic renal disease, persistent proteinuria (urinary protein excretion > 0.3g/24hrs), no history of allergic reaction to medications, including ACEIs	Losartan titrated every 3-4 weeks until 100mg daily (25mg 8a.m., 25mg 12p.m., 50mg 5p.m.) with placebo; trandolapril 3mg once daily with placebo twice daily; combination of both drugs at the same doses Mean follow-up 2.9 years
Lacourciere, 2000 Canada (Poor)	Multicenter	Male and female outpatients with type 2 diabetes mellitus diagnosed at 30 years of age or later; mild to moderate essential hypertension (sitting diastolic BP (SIDBP) 90 to 115 mm Hg); early nephropathy characterized by a UAE rate 20 to 350 µg/min without evidence of urinary tract infection	Losartan 50 mg once daily; doubled at week 8 if SIDBP > 85 mm Hg Enalapril 5 mg once daily; titrated to 10 mg if SIDBP > 95 mm Hg at 4 weeks; doubled at week 8 if SIDBP > 85 mm Hg *Early up-titration was permitted starting at week 4 for patients having SIDBP > 105 mm Hg* *Duration 1 year*

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Nakao, 2003 Japan COOPERATE (Good)	All antihypertensive agents including ACEIs were discontinued for 3 weeks; 301 patients received single-blind run-in of trandolapril 0.5mg increased to 6mg for 18 weeks to determine maximum dose for renoprotection (e.g., mean percent change in daily excretion urinary protein reached plateau with 3mg); trandolapril was then discontinued for 3 weeks	Antihypertensive agents (excluding ACEIs and AIIRAs) used to achieve BP < 130/80 mm Hg
Lacourciere, 2000 Canada (Poor)	Antihypertensive medications (other than beta blockers and/or nitrates for stable angina) were discontinued during a 7-day washout period 2-4 week single-blind placebo run-in period	HCTZ 12.5 mg titrated to 25 mg to achieve a goal SIDBP of 85 mm Hg starting at week 12 Additional antihypertensive agents other than ACE inhibitors, AIIRAs, CCBs then added

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Nakao, 2003 Japan COOPERATE (Good)	Primary endpoint included composite doubling sCr or ESRD (GFR < 7ml/min/1.73m2 or dialysis); secondary endpoint was to assess change in BP, daily urinary protein excretion, and to note any adverse reactions. Patients examined by nephrologist every month for first 6 months, then every 3 months. Patients collected 24hr urine samples, 3 days prior to visits; trained nurses measured supine BP after 15 min rest	Mean age 45 47% male, 100% Japanese	65% glomerular renal disease, 18% HTN, GFR 38ml/min, sCr 267umol/l, urinary protein excretion 2.5g/day (22% $\geq$ 3g/d, 40% 1-3g/d, 38% < 1g/d), BP 130/75 mm Hg, median 3 antihypertensive agents
Lacourciere, 2000 Canada (Poor)	Laboratory evaluations performed after 4, 12, 28 and 52 weeks	58.5 80.1% male 96.1% white	SIDBP=160.0 DIDBP=96.3 Weight (kg)=91.9 Diabetes duration (years)=10.9 Age at diabetes diagnosis (years)=47.4 Urinary albumin excretion (geometric means)=68.9

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Nakao, 2003 Japan COOPERATE (Good)	336 screened/306 eligible/263 enrolled	Unable to determine number withdrawn/7 lost to follow-up/256 analyzed for primary endpoint	**Primary endpoint (composite doubling sCr or ESRD):** losartan 23% (20 of 86) vs. combination 11% (10 of 85) HR 0.40 (95% CI 0.17-0.69; P=0.016), NNT=9 Cox model (95% CI 4-420); trandolapril 23% (20 of 85) HR 0.38 (95% CI 0.18-0.63; P=0.018) NNT=8 Cox model (95% CI 4-227). Benefit of combination therapy seen regardless of baseline urinary protein excretion rate
Lacourciere, 2000 Canada (Poor)	Number screened not reported/number eligible not reported/103 enrolled	10(10.7%) withdrawn/number lost to fu not reported/98(95.1%) analyzed	Albuminuria change (%) Losartan=35.2% Enalapril=54.7% NS Glomerular filtration rate (GFR) change (%) Losartan=9% reduction Enalapril=9% reduction NS

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Nakao, 2003 Japan COOPERATE (Good)	**Secondary endpoints:** maximal median change in daily urinary protein excretion: losartan -42.1%, trandolapril -44.3%, combination -75.6% (P=0.01 vs. baseline); mean change BP vs. baseline: losartan -5.1±1.6/-2.9±0.9 mm Hg, trandolapril -5.2±1.3/-2.9±0.8 mm Hg, combination -5.3±1.4/-3.0±0.7 mm Hg (decrease similar for all groups; P=0.109)	Not reported	Total adverse reactions: losartan 12% (11/89), trandolapril 22% (19/86), combination 21% (18/88); dry cough: losartan 1%, trandolapril 5.8%, combination 5.7%; hyperkalemia: losartan 4.5%, trandolapril 9.3%, combination 8.0%; sudden death occurred in 1 patient on losartan (thought to be related to rupture of abdominal aneurysm); non-fatal CV event: losartan 2.3%, trandolapril 3.5%, combination 3.4%
Lacourciere, 2000 Canada (Poor)		Not reported	Cough Losartan 0% Enalapril 14%; (P=0.006) Uric acid concentration change Losartan (-22.0) µmol/L Enalapril (+12.0) µmol/L; (P=0.001)

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Nakao, 2003 Japan COOPERATE (Good)	5 patients discontinued treatment/unable to determine withdrawals due to adverse events	Trial stopped early (anticipated 5yr follow-up) due to significant benefit with combination therapy. Independent risk factors for combined primary endpoint: combination therapy, age, baseline renal function, change in daily urinary protein excretion rate, antiproteinuric response to trandolapril, use of diuretics
Lacourciere, 2000 Canada (Poor)	Total withdrawals Losartan 6/49(12.2%) Enalapril 5/49(10.2%) Adverse event withdrawals Losartan 2/49(4.1%) Enalapril 1/49(2%)	

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Study Design (optional) Setting	Eligibility criteria	Interventions (drug, dose, duration)
Luno, 2002 Spain (Fair)	Multicenter, open	Male and female outpatients between 18 and 80 years old with primary proteinuric nephropathies for more than 6 months; patients were included irrespective of their BP if proteinuria measured by the sulfosalicylic acid method was greater than 2 g in at least two 24-hour urine collections and the GFR, estimated by CrCl > 50 mL/min/1.73 m2	Lisinopril 10-40 mg once daily Candesartan 8-32 mg once daily Lisinopril 5-20 mg + Candesartan 4-16 mg After 2 weeks, dosage doubled every 2 weeks up to maximum dose (above) if SBP > 125 mm Hg or DBP > 75 mm Hg Duration 6 months
Muirhead, 1999 Canada (Fair)	Multicenter	Male and female outpatients ≥ 18 years of age, of any racial background with type 2 DM and incipient diabetic nephropathy (defined as AER between 20 and 300 mg/min with GFR ≥ 60 mL/min per 1.73 m2); normotensive and treated hypertensive patients with a sitting DBP ≤ 95 mm Hg and a sitting SBP ≤ 160 mm Hg	Valsartan 80 mg once daily Valsartan 160 mg once daily Captopril 25 mg three times daily Placebo Duration 1 year

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Luno, 2002 Spain (Fair)	2-week washout	Antihypertensive medication, such as beta blockers, CCBs and/or thiazide diuretics along or in combination were subsequently introduced from weeks 6 to 12 in order to achieve goal of BP <125/75 mm Hg
Muirhead, 1999 Canada (Fair)	28-day washout of ACE inhibitors and CCBs	Customary medication, diuretics, beta blockers

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Luno, 2002 Spain (Fair)	Study visits at 2 4, 6, 8, 12 and 24 weeks after randomization	45 68.7% male Ethnicity not reported	BMI 26.7 kg/m2 SBP 134 mm Hg DBP 81 mm Hg Albumin 3.6 g/dL CrCl 95 mL/min
Muirhead, 1999 Canada (Fair)	Clinic visits at weeks 6, 12, 26, 38, and 52	56 72.9% male 90.2% white	Body weight 94.4 kg SSBP 135.6 mm Hg SDBP 83.1 mm Hg AER 56.1 ug/min GFR 89.9 mL/min per 1.73 m2

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Luno, 2002 Spain (Fair)	Number screened not reported/number eligible not reported/46 enrolled	1(2.2%) withdrawn/number lost to fu not reported/45 analyzed	CrCl change Candesartan 7.7% decrease Lisinopril 2.4% increase Candesartan+Lisinopril: no change NS
Muirhead, 1999 Canada (Fair)	Number screened not reported/number eligible not reported/122 enrolled	19(15.6%) withdrawn/0 lost to fu/114 analyzed for GFR; 120 analyzed for AE	AER (µg/min) Valsartan 80 mg 27.8% decrease (P=0.018 vs.placebo) Valsartan 160 mg 21.2% decrease Captopril 26.4% decrease (P=0.009 vs. placebo) Placebo 18.2% increase Valsartan vs. captopril (NS) GFR change (%) Valsartan 80 mg 7.2% decrease Valsartan 160 mg 10.6% decrease Captopril 0.4% increase Placebo 7.7% decrease NS

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Luno, 2002 Spain (Fair)		Adverse events were recorded at each visit in response to open questions or as observed in investigators	Not reported
Muirhead, 1999 Canada (Fair)		Not reported	<u>Total patients with ≥ 1 AE</u> Valsartan 80 mg 9.7% Valsartan 160 mg 22.6% Captopril 34.5% Placebo 13.8% <u>Dry Cough</u> Valsartan 80 mg 3.2% Valsartan 160 mg 9.7% Captopril 20.7% Placebo 3.4%

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Luno, 2002 Spain (Fair)	Not reported	Doses used in the combination group were half that of the monotherapy groups
Muirhead, 1999 Canada (Fair)	Total withdrawals Valsartan 80 mg 22.6% Valsartan 160 mg 3.2% Captopril 13.8% Placebo 22.6% Total withdrawals due to adverse events Valsartan 80 mg 3.2% Valsartan 160 mg 3.2% Captopril 6.9% Placebo 0%	

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Study Design (optional) Setting	Eligibility criteria	Interventions (drug, dose, duration)
Andersen, 2000 Denmark (Fair)	RCT, cross-over	Male and females age 18 to 70 years with a diagnosis of type 1 DM and nephropathy (diagnosed in patients with persistent albuminuria ≥ 300mg/24h, diabetic retinopathy, DM > 10 years, and absence of clinical or laboratory evidence of other kidney disease), GFR > 60mL/min/1.73m2, BP > 145/85 mm Hg	Losartan 50mg, losartan 100mg, enalapril 10mg, enalapril 20mg, or placebo each for 2 months
Campbell, 2003 Italy (Fair)	RCT, open, cross-over	Male and females age ≥ 18 years with HTN and chronic renal disease (CrCl 20-70mL/min/1.73m2 and urinary protein excretion rate ≥ 1gm/24h)	Randomized to 1 of 6 treatment sequences consisting of valsartan alone, benazepril alone, or the combination, each for 8 weeks. Dose level 1 (valsartan 80mg, benazepril 10mg, or valsartan 40mg plus benazepril 5mg) for 2 weeks then dose level 2 (valsartan 160mg, benazepril 20mg, or valsartan 80mg plus benazepril 10mg) for remaining 8 weeks (if hyperkalemia or symptomatic hypotension, dose decreased to level 1)

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/interventions
Andersen, 2000 Denmark (Fair)	All antihypertensive agents were discontinued for at least 4 weeks	Five patients received furosemide during all treatment periods for prevention of peripheral edema, no other concomitant medications given
Campbell, 2003 Italy (Fair)	All AIIRAs, ACEIs, and potassium-sparing diuretics discontinued for 8 weeks	Clonidine or loop or thiazide diuretics used as needed to achieve DBP $\leq$ 90 mm Hg

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity		Other population characteristics (diagnosis, etc)
Andersen, 2000 Denmark (Fair)	Objective to evaluate short-term renoprotective effect of AIIRA and compare renal and hemodynamic effects vs. ACEI; GFR (180, 200, 220, 240 min after IV injection 3.7 MBq Cr-EDTA), 24-hour ambulatory BP (Takeda TM2420, every 15 min 7a.m.-11p.m., every 30min 11p.m.-7a.m.), albuminuria (by ELISA) measured at end of each 2 month treatment	Mean age 42	10 males, 6 females (ethnicity not specified)	Duration of DM 33yrs, albuminuria 1156mg/24hr, GFR 90ml/min/1.73m2, BP 147/82 mm Hg, 24hr MAP 104 mm Hg
Campbell, 2003 Italy (Fair)	Objective to compare reduction in proteinuria with half doses AIIRA plus ACEI vs. either drug alone at higher doses; 24hr urinary protein (average of three 24hr urine collections during 3 days prior to clearance studies), urinary protein/Cr and CrCl (measured from last 24hr urine collection), GFR (inulin and para-aminohippuric acid loading dose followed by 130mg/kg dextran 40 with average of 3 measurements 40min apart after 40min equilibrium period), BP (3 measurements by automated cuff prior to clearance studies)	Mean age 49	23 males, 1 female (Caucasian)	46% IgA nephritis, 24 hr urinary protein 3.28g/24hrs, urinary protein/Cr 1.89, sCr 1.67mg/dL, CrCl 69ml/min, GFR 46.5ml/min/1.73m2, BP 140/91 mm Hg, MAP 107 mm Hg

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Andersen, 2000 Denmark (Fair)	Number screened not reported/number eligible not reported/16 enrolled	none withdrawn/none lost to fu/16 analyzed	Albuminuria: losartan 50mg reduced by 33% (95% CI 12-51) vs. placebo, losartan 100mg reduced by 44% (95% CI 26-57) vs. placebo, enalapril 10mg reduced by 45% (95% CI 23-61) vs. placebo, enalapril 20mg reduced by 59% (95% CI 39-72) vs. placebo (all P<0.05 vs. placebo); GFR remained stable with all treatments: losartan 50mg 91±6 ml/min per 1.73m2, losartan 100mg 89±6 ml/min per 1.73m2, enalapril 10mg 89±6 ml/min per 1.73m2, enalapril 20mg 87±6ml/min per 1.73m2, placebo 90±6 ml/min per 1.73m2
Campbell, 2003 Italy (Fair)	Number screened not reported/number eligible not reported/24 enrolled	none withdrawn/none lost to fu/24 analyzed	24hr urinary protein excretion: valsartan + benazepril 1.39+1.54g/24hr (P<0.01 vs. 2.04+2.36g/24hr with valsartan alone; P<0.05 vs. 1.76+1.88g/24hr with benazepril alone), reduced from baseline by 56% with valsartan + benazepril (P=0.002 vs. 41.5% reduction from baseline with valsartan alone; P=0.024 vs. 45.9% reduction from baseline with benazepril alone); GFR: baseline 46.5±12.8ml/min/1.73m2, valsartan + benazepril 48.1+17.1ml/min/1.73m2, valsartan alone 47.9+14.6ml/min/1.73m2, benazepril alone 47.7+13.5ml/min/1.73m2 (difference in percent change from baseline not significant)

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported
Andersen, 2000 Denmark (Fair)	24hr MAP decreased from 104±2 mm Hg with placebo vs. 95±2 mm Hg with losartan 50mg, 96±2 mm Hg with losartan 100mg, 98±3 mm Hg with enalapril 10mg, and 93±3 mm Hg with enalapril 20mg (all P<0.05 vs. placebo); all 24hr SBP/DBP reduced with all treatments vs. placebo (P<0.05)	Not reported	No reported side effects related to losartan or enalapril; serum potassium increased to 4.31±0.1 mmol/L with enalapril 10mg, 4.29±0.1mmol/L with enalapril 20mg, vs. 4.00±0.1 mmol/L with placebo (P<0.05), difference not significant with losartan 50mg (4.18±0.1mmol/L), losartan 100mg (4.13±0.1mmol/L) vs. placebo; sCr: difference not significant vs. placebo (96±5 umol/L), losartan 50mg (94±5 umol/L), losartan 100mg (92±7 umol/L), enalapril 10mg (96±5 umol/L), enalapril 20mg (89±6 umol/L)
Campbell, 2003 Italy (Fair)	MAP decreased from 107±8 mm Hg at baseline to 94±10 mm Hg with valsartan + benazepril, 95±8 mm Hg with valsartan alone, 95±8 mm Hg with benazepril alone (difference in percent change from baseline not significant)	Standard lab techniques for blood chemistries taken prior to clearance studies	Side effects other than changes in laboratory parameters not reported. Serum potassium increased from baseline (4.1+0.56 mEq/L) to 4.63±0.42 mEq/L with valsartan + benazepril, 4.33+0.37 mEq/L with valsartan alone, 4.45+0.39 mEq/L with benazepril alone (P<0.05 combination vs. either valsartan or benazepril alone); no statistically significant change in sCr or CrCl

Evidence Table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Andersen, 2000 Denmark (Fair)	All patients completed the study	Unable to determine long-term effect with 2 month treatment periods. No significant correlations between BP changes in each patient and albuminuria. Authors report the possibility of a type 2 error comparing the antiproteinuric effect of losartan and enalapril at the higher doses
Campbell, 2003 Italy (Fair)	All patients completed the study	Unable to determine long-term effect with 2 month treatment periods. Doses used in the combination group were half that of the monotherapy groups

Evidence Table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout Period
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT (Good)	RCT, multicenter	Age between 30 and 70 years, documented diagnosis of type 2 DM, HTN (SBP> 135 mm Hg, DBP > 85 mm Hg, or antihypertensive treatment), proteinuria (urinary protein excretion at least 900mg/24hrs), sCr 1.0-3.0mg/dl (women) or 1.2-3.0mg/dl (men)	Irbesartan 75mg titrated to 300mg daily, amlodipine 2.5mg titrated to 10mg daily, or placebo Mean follow-up 2.6 years	All ACEIs, AIIRAs, CCBs were discontinued 10 days prior to randomization (BP was controlled by alternate antihypertensive agents during this time)
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL (Good)	RCT, multicenter	Male and females age 31 and 70 years with a diagnosis of type 2 DM and nephropathy (defined as ratio urinary albumin to urinary creatinine $\geq$ 300mg/l and sCr 1.3-3.0mg/dl (lower limit 1.5mg/dl for patients > 60kg)	Losartan 50mg titrated to 100mg daily after 4 weeks if BP $\geq$140/90 mm Hg or placebo Mean follow-up 3.4 years	All ACEIs and AIIRAs were discontinued 6 weeks prior to randomization and replaced by alternate antihypertensive agents

Evidence Table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

Author Year Country Trial Name (Quality Score)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT (Good)	Antihypertensive agents other than ACEIs, AIIRAs, or CCBs to achieve target BP (SBP ≤ 135 mm Hg or 10 mm Hg lower if screening SBP > 145 mm Hg; DBP ≤ 85 mm Hg); 58% on insulin at baseline	Primary endpoint included composite doubling sCr, onset of ESRD (initiation of dialysis, renal transplantation, or sCr ≥ 6.0mg/dl), or all-cause mortality; secondary CV endpoint included composite CV death, nonfatal MI, HF hospitalization, a permanent neurologic deficit due to stroke, or above the ankle lower limb amputation. Mortality, ESRD, CV endpoints, sCr and potassium, and 24hour urinary protein excretion were monitored quarterly	Mean age 59 64% male, 73% white, 14% black, 5% Hispanic, 5% Asian or Pacific Islander, 4% other
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL (Good)	Antihypertensive agents other than ACEIs or AIIRAs to achieve target BP (SBP ≤ 140 mm Hg and DBP ≤ 90 mm Hg); 78% on CCBs, 84% on diuretics; standard of care for DM	Primary endpoint included time to first event composite doubling sCr (first sCr that was twice baseline, confirmed at least 4 weeks later), ESRD (need for chronic or renal transplantation), or all-cause mortality; secondary endpoint included CV morbidity and mortality (composite MI, stroke, first hospitalization for HF or unstable angina, coronary or peripheral revascularization, or death from CV causes); progression of renal disease and changes in level of proteinuria. Follow-up was scheduled for every 3 months	Mean age 60 63% male, 48% white, 15% black, 18% Hispanic, 16% Asian

Evidence Table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT (Good)	29% CV disease, sCr 1.67mg/dl, HbA1c 8.2%, BP 159/87 mm Hg	Number screened not reported/number eligible not reported/1715 enrolled	16 never received study drug/11 lost to follow-up/1715 analyzed
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL (Good)	93.5% receiving antihypertensive medications (additional 3% with HTN not on medications), BP 152/82 mm Hg, sCr 1.9mg/dl, HbA1c 8.5%	Number screened not reported/number eligible not reported/1513 enrolled	46.5% on losartan and 53.5% on placebo discontinued treatment/3 lost to follow-up/1513 analyzed

Evidence Table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

Author Year Country Trial Name (Quality Score)	Results	Results
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT (Good)	**Primary endpoint (composite doubling sCr, onset of ESRD, or all-cause mortality) at 2.6 years:** irbesartan vs. placebo RR 0.80 (95% CI 0.66-0.97; P=0.02), [calculated RR 0.84 (95% CI 0.72-0.98), calculated NNT=16 (95% CI 8-119) based on crude rates of events, irbesartan 189/579 (32.6%) vs. placebo 222/569 (39%)]; irbesartan vs. amlodipine RR 0.77 (95% CI 0.63-0.93; P=0.006), calculated NNT=12 (95% CI 7-35); When analyzed separately, doubling baseline sCr decreased with irbesartan vs. placebo (P=0.003) and vs. amlodipine (P<0.001), decrease in ESRD and decrease all-cause mortality with irbesartan not statistically significant vs. placebo or vs. amlodipine	**Secondary endpoints:** composite CV endpoint: irbesartan vs. placebo RR 0.91 (95% CI 0.72-1.14; P=0.40); irbesartan vs. amlodipine RR 1.03 (95% CI 0.81-1.31; P=0.79); changes in renal function: sCr increased 24% more slowly with irbesartan vs. placebo (P=0.008), sCr mean absolute rates of change were 0.45±0.04mg/dl/yr with irbesartan vs. 0.59±0.04mg/dl/yr with placebo, mean rate of change in CrCl was -5.5±0.36 ml/min per 1.73m2 with irbesartan vs. -6.5±0.37 ml/min per 1.73m2 in the placebo group
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL (Good)	**Primary endpoint (composite doubling sCr, onset of ESRD, or all-cause mortality) at 3.4 years:** losartan vs. placebo RR 0.84 (95% CI 0.72-0.98; P=0.02 based on results from Cox regression model) [calculated RR 0.92 (95% CI 0.83-1.03), NNT not calculable based on crude rates of events, losartan 327/751 (43.5%) vs. placebo 359/762 (47.1%)]; when analyzed separately, doubling baseline sCr decreased with losartan vs. placebo (P=0.006) calculated NNT=23 (95% CI 11-773) as did ESRD (P=0.002) calculated NNT=17 (95% CI 10-59), slight increase in all-cause mortality with losartan was not statistically significant (P=0.88)	**Secondary endpoints:** losartan vs. placebo: composite CV endpoint RR 0.90 (P=0.26); changes in renal function: losartan reduced the rate of decline (reciprocal of sCr concentration) by 18% vs. placebo (P=0.01), and 15.2% reduction in the estimated decline in GFR (median rate of decline 4.4ml/min per 1.73m2 with losartan vs.5.2ml/min per 1.73m2 in the placebo group, P=0.01)

Evidence Table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT (Good)	Protocol established for management of hyperkalemia and to detect early rises in sCr (to assess for renal artery stenosis)	Discontinuation due to hyperkalemia: irbesartan (1.9%), amlodipine (0.5%), placebo (0.4%) (P=0.01 for both comparisons); one episode of early rise in sCr suggestive of renal artery stenosis led to discontinuation of study drug (medication not specified); irbesartan had a lower rate of adverse events/1000 treatment days vs. amlodipine or placebo (P=0.002)	23.7% of patients discontinued treatment/withdrawals due to adverse events not reported although stated that most common reason for discontinuation was clinical CV event	Not powered to detect difference in all-cause mortality or composite CV endpoint. Average MAP was 3.3 mm Hg lower in the irbesartan and amlodipine groups compared to placebo (P=0.001), MAP was not significantly different between irbesartan and amlodipine
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL (Good)	Elicited by investigator at study visit	Discontinuation due to increased sCr or hyperkalemia: losartan (1.5%, 1.1%, respectively) vs. placebo (1.2%, 0.5%, respectively)	46.5% of patients on losartan discontinued treatment (53.5% on placebo)/withdrawals due to adverse events occurred in 17.2% on losartan and 21.7% on 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 BP

Evidence Table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout Period
Plum, 1998 Country not reported (Fair)	RCT	Arterial HTN, sitting DBP < 105 mm Hg and SBP < 180 mm Hg at visit 4; stable renal insufficiency with a sCr between 200 and 600 mmol/L; stable proteinuria of at least 500 mg/24 h	Valsartan 80 mg once daily Placebo Duration 6 months	3-month run-in - intervention not reported

Evidence Table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

Author Year Country Trial Name (Quality Score)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Plum, 1998 Country not reported (Fair)	Beta blockers, alpha blockers, CCBs, clonidine, minoxidil, furosemide	Examinations every 4 weeks	59 66.7% male Ethnicity not reported

Evidence Table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Plum, 1998 Country not reported (Fair)	Weight 82 kg Height 170.8 cm Mean arterial pressure 114.2 mm Hg sCr 356.5 mmol/L Proteinuria 1346 mg/d	Number screened not reported/number eligible not reported/9 enrolled	1(11.1%) withdrawn/0 lost to fu/9 analyzed

Evidence Table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

Author Year Country Trial Name (Quality Score)	Results	Results
Plum, 1998 Country not reported (Fair)	Albuminuria change (%) Valsartan 41% decrease Placebo 9.8% increase P<0.05 after 6 months GFR change (%) Valsartan 10% decrease Placebo 10% increase NS after 6 months	

Evidence Table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Plum, 1998 Country not reported (Fair)	Not assessed	Uric acid concentration change Valsartan increase 24 µmol/L (5.6%) Placebo increase 40 µmol/L (8.3%)	Total withdrawals Valsartan 1/5(20%) Placebo 0	

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Tedesco, 1999 Country not stated (Fair)	Hypertension	Losartan 50mg	HCTZ 25mg	2.2 years	69
Dahlof, 1997 Sweden, Australia, Finland LOA Study (Fair)	Hypertension	Losartan up to 100mg	Losartan 50mg + HCTZ 12.5mg Amlodipine up to 10mg	12 weeks	898
Tanser, 1998 Australia, Canada, Europe, Mexico (Fair)	Hypertension	Candesartan 8mg	Enalapril 10mg Placebo	8 weeks	156
Rake, 2001 U.S. (Fair)	Hypertension	Eprosartan 1200mg Enalapril 20 mg once daily Placebo	Enalapril 20mg Placebo	6 weeks	136

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Tedesco, 1999 Country not stated (Fair)	None	No complaints of cough or complications in sexual performance; no adverse laboratory events reported
Dahlof, 1997 Sweden, Australia, Finland LOA Study (Fair)	Losartan (2%) Amlodipine (8%) Losartan + HCTZ (5%) (losartan vs. amlodipine; P=0.01)	Any discomfort Losartan (22.5%) Losartan + HCTZ (23.5%) Amlodipine (33.1%) Dizziness upon standing Losartan (10.1%) Losartan + HCTZ (17.1%) Amlodipine (33.1%)
Tanser, 1998 Australia, Canada, Europe, Mexico (Fair)	Candesartan (8.1%) Enalapril (4.5%) Placebo (11.5%)	Cough Candesartan (16%) Enalapril (31%) Placebo 11%
Rake, 2001 U.S. (Fair)	Not reported	Self-assessed cough *All coughs* Placebo=2/41(4.9%) Enalapril=9/39(23.1%)(p=0.047 for eprosartan vs enalapril) Eprosartan=2/39(5.1%)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Tedesco, 1999 Country not stated (Fair)	
Dahlof, 1997 Sweden, Australia, Finland LOA Study (Fair)	
Tanser, 1998 Australia, Canada, Europe, Mexico (Fair)	
Rake, 2001 U.S. (Fair)	Investigator reported cough Placebo=3/41(7.3%) Enalapril=11/39(28.2%)NS Eprosartan=5/39(12.8%)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Breeze, 2001 North America, Europe, South Africa (Fair)	Hypertension	Eprosartan 800-1200mg	Enalapril 5-20mg Placebo	26 weeks	529
De Rosa, 2002 Italy (Fair)	Hypertension	Losartan 12.5-50mg	Enalapril 5-20mg Placebo	3 years	50
Lithell, 2003 U.S., Canada, Europe SCOPE trial (Fair)	Hypertension	Candesartan 8-16mg (addition of HCTZ 12.5mg and open-label antihypertensive treatment as needed)	Placebo (addition of HCTZ 12.5mg and open-label antihypertensive treatment as needed)	3.7 years	4937
Parving, 2001 Canada, Europe, South America, South Africa (Fair)	Hypertension	Irbesartan 150mg Irbesartan 300mg	Placebo	2 years	611

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Breeze, 2001 North America, Europe, South Africa (Fair)	Withdrawal due to cough Eprosartan (0.7%) Enalapril (2.6%)	Cough incidence *Study endpoint analysis* *Definite/Probable/possible* Eprosartan (3.2%) Enalapril (7.6%)
De Rosa, 2002 Italy (Fair)	Losartan 0 Enalapril (12.5%) NS	Incidence of bother due to cough Losartan 2% Enalapril 12% (P=0.01)
Lithell, 2003 U.S., Canada, Europe SCOPE trial (Fair)	Candesartan (15%) Control (17%)	Hypotension Candesartan (24.6%) Control (23.4%) Dizziness/vertigo Candesartan (20.9%) Control (20.0%)
Parving, 2001 Canada, Europe, South America, South Africa (Fair)	Irbesartan 150mg (9.2%) Irbesartan 300mg (4.1%) Placebo 17/201(8.4%)	Serious adverse events Irbesartan150/300 (15.4%) Placebo (22.8%) (P=0.02)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Breeze, 2001 North America, Europe, South Africa (Fair)	Monotherapy endpoint analysis *Definite/Probable/possible* Eprosartan (2.0%) Enalapril (9.7%) (p=0.001)
De Rosa, 2002 Italy (Fair)	
Lithell, 2003 U.S., Canada, Europe SCOPE trial (Fair)	Increase sCr Candesartan (91.0 to 100.6umol/l) Control (91.0 to 96.3 umol/l)
Parving, 2001 Canada, Europe, South America, South Africa (Fair)	

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial (Good)	High CV risk factors	Losartan 50-100mg (± HCTZ 12.5mg)	Atenolol 50-100mg (± HCTZ 12.5mg)	4.8 years	9193
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease) (Good)	High CV risk factors	Losartan 50-100mg (± HCTZ 12.5mg)	Atenolol 50-100mg (± HCTZ 12.5mg)	4.8 years	6886
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH) (Good)	High CV risk factors	Losartan 50-100mg (± HCTZ 12.5mg)	Atenolol 50-100mg (± HCTZ 12.5mg)	4.7 years	1326

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial (Good)	Losartan13% Atenolol 18% (P<0.0001)	Hypotension Losartan (3%) Atenolol (2%) (P=0.001) Cough Losartan (3%) Atenolol (2%)
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease) (Good)	Not reported	Any adverse event Losartan (12.7%) Atenolol (17.3%) (P<0.001) Drug-related adverse event Losartan (6.0%) Atenolol (10.2%) (P<0.001)
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH) (Good)	Losartan14.6% Atenolol 22.1% (P<0.001)	Hypotension Losartan (4.4%) Atenolol (2.7%) Cough Losartan (4.1%) Atenolol (2.9%)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial (Good)	Angioedema Losartan (0.1%) Atenolol (0.2%) Potassium Losartan (0.0+0.4mmol/L) Atenolol (decreased 0.1+0.5mmol/L)
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease) (Good)	Serious adverse event Losartan (3.8%) Atenolol (4.4%) Serious, drug-related adverse event Losartan (0.5%) Atenolol (1.0%) (P=0.018)
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH) (Good)	Angioedema Losartan (0.3%) Atenolol (0.3%) Potassium Losartan (-0.002mEq/L) Atenolol (-0.08mEq/L)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM) (Good)	High CV risk factors	Losartan 50-100mg (± HCTZ 12.5mg)	Atenolol 50-100mg (± HCTZ 12.5mg)	4.7 years	1195
Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial (Good)	Recent MI	Valsartan 320mg	Captopril 150mg Valsartan 160mg + Captopril 150mg	2.1 years	14,808

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM) (Good)	Not reported	Hypotension Losartan (2%) Atenolol (1%) Cough Losartan (4%) Atenolol (3%)
Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial (Good)	Valsartan (5.8%) Captopril (7.7%) Valsartan + captopril (9.0%) (Valsartan vs. captopril, valsartan + captopril vs. captopril; P<0.05)	Hypotension (requiring dose reduction) Valsartan (15.1%) Captopril (11.9%) Valsartan + captopril (18.2%) Cough (requiring dose reduction) Valsartan (1.7%) Captopril (5.0%) Valsartan + captopril (4.6%) Angioedema (requiring dose reduction) Valsartan (0.2%) Captopril (0.5%) Valsartan + captopril (0.5%)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM) (Good)	Angioedema Losartan (0.2%) Atenolol (0.5%) Potassium Losartan (0.05mmol/L) Atenolol (no change)
Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial (Good)	Renal causes (requiring dose reduction) Valsartan (4.9%) Captopril (3.0%) Valsartan + captopril (4.8%) Hyperkalemia (requiring dose reduction) Valsartan (1.3%) Captopril (0.9%)Captopril (0.9%) Valsartan + captopril (1.2%)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAAL trial (Good)	Recent MI	Losartan 50mg	Captopril 150mg	2.7 years	5477
Nakao, 2003 Japan COOPERATE (Good)	Nephropathy	Losartan 100mg	Trandolapril 3mg Losartan 100mg + Trandolapril 3mg	2.9 years	263
Lacourciere, 2000 Canada (Poor)	Nephropathy	Losartan 50-100mg	Enalapril 5-10mg	1 year	103

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events		Adverse Effects Reported
Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAAL trial (Good)	Losartan 7% Captopril 14%	(P<0.0001)	Hypotension Losartan (13.3%) Captopril (16.3%) Cough Losartan (9.3%) Captopril (18.7%) (P<0.0001)
Nakao, 2003 Japan COOPERATE (Good)	Not reported		Total adverse reactions Losartan (12%) Trandolapril (22%) Combination (21%) Dry cough Losartan (1%) Trandolapril (5.8%) Combination (5.7%)
Lacourciere, 2000 Canada (Poor)	Losartan (4.1%) Enalapril (2%)		Cough Losartan (0%) Enalapril (14%); (P=0.006) Uric acid concentration change Losartan (-22.0 µmol/L) Enalapril (+12.0 µmol/L); (P=0.001)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAAL trial (Good)	Angioedema (requiring dose reduction) Losartan (0.4%) Captopril (0.8%) Potassium (change from baseline) Losartan (0.19mmol/L) Captopril (0.22mmol/L) (P=0.01)
Nakao, 2003 Japan COOPERATE (Good)	Hyperkalemia Losartan (4.5%) Trandolapril (9.3%) Combination (8.0%)
Lacourciere, 2000 Canada (Poor)	

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Luno, 2002 Spain (Fair)	Nephropathy	Candesartan 8-32mg	Candesartan 8-32mg Candesartan 4-16 mg + Lisinopril 5-20mg	6 months	46
Muirhead, 1999 Canada (Fair)	Nephropathy	Valsartan 80mg Valsartan 160mg	Captopril 75 mg Placebo	1 year	122
Anderson, 2000 Denmark (Fair)	Nephropathy	Losartan 50mg Losartan 100mg	Enalapril 10mg Enalapril 20mg Placebo	8 months	16

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Luno, 2002 Spain (Fair)	Not reported	Not reported
Muirhead, 1999 Canada (Fair)	Valsartan 80mg 3.2% Valsartan 160mg 3.2% Captopril 6.9% Placebo 0%	Total patients with ≥ 1 AE Valsartan 80 mg (9.7%) Valsartan 160 mg (22.6%) Captopril (34.5%) Placebo (13.8%) Dry Cough Valsartan 80 mg (3.2%) Valsartan 160 mg (9.7%) Captopril (20.7%) Placebo (3.4%)
Anderson, 2000 Denmark (Fair)	None	Potassium (level increased to) Losartan 50mg (4.18±0.1mmol/L) Losartan 100mg (4.13±0.1mmol/L) Enalapril 10mg (4.31±0.1 mmol/L) Enalapril 20mg (4.29±0.1mmol/L) Placebo (4.00±0.1 mmol/L) Losartan vs. placebo (NS)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Luno, 2002 Spain (Fair)	
Muirhead, 1999 Canada (Fair)	
Anderson, 2000 Denmark (Fair)	

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT (Good)	Nephropathy	Irbesartan 300mg	Amlodipine 10mg Placebo	2.6 years	1715
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL (Good)	Nephropathy	Losartan 50-100mg	Placebo	3.4 years	1513
Plum, 1998 Country not reported (Fair)	Nephropathy	Valsartan 80mg	Placebo	6 months	9
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	Heart Failure	Losartan up to 50mg	Captopril up to 150mg	1.5 years	3152

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT (Good)	Not reported	Hyperkalemia (discontinued) Irbesartan (1.9%) Amlodipine (0.5%) Placebo (0.4%) (P=0.01 for both comparisons) Irbesartan lower rate of adverse events/1000 treatment days vs. amlodipine or placebo (P=0.002)
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL (Good)	Losartan (17.2%) Placebo (21.7%)	Discontinuation due to increased sCr Losartan (1.5%) Placebo (1.2%) (P=0.01) Discontinuation due to hyperkalemia Losartan (1.1%) Placebo (0.5%) (P=0.01)
Plum, 1998 Country not reported (Fair)	Not reported	Uric acid concentration change Valsartan + 24 μmol/L (5.6%) Placebo + 40 μmol/L (8.3%)
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	Losartan (~10%) Captopril (~15%) (P<0.001)	Withdrawals due to cough Losartan (~1%) Captopril (~3%) (P<0.001)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT (Good)	
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL (Good)	
Plum, 1998 Country not reported (Fair)	
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	Heart Failure	Losartan up to 50mg	Captopril up to 150mg	48 weeks	722
Houghton, 1999 U.K. ELITE Trial substudy (Fair)	Heart Failure	Losartan up to 50mg	Captopril up to 150mg	24 weeks	18
Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	Heart Failure	Losartan up to 50mg	Captopril up to 150mg	48 weeks	278
Willenheimer, 2002 Sweden HEAVEN Study (Fair)	Heart Failure	Valsartan 160mg	Enalapril 20mg	12 weeks	146

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	Losartan (12.2%) Captopril (20.8%) (P≤0.002)	Withdrawals due to cough Losartan (0%) Captopril (3.8%) (P<0.002) Withdrawals due to angioedema Losartan (0%) Captopril (0.8%)
Houghton, 1999 U.K. ELITE Trial substudy (Fair)	Losartan (0) Captopril (37.5%)	Not reported
Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	Losartan (10.9%) Captopril (19.0%)	Not reported
Willenheimer, 2002 Sweden HEAVEN Study (Fair)	Valsartan (2.9%) Enalapril (4.2%)	All adverse events Valsartan (50%) Enalapril (63%) Headache Valsartan (5.7%) Enalapril (1.4%)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	Withdrawals due to hyperkalemia Losartan (0.6%) Captopril (1.6%)
Houghton, 1999 U.K. ELITE Trial substudy (Fair)	
Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	
Willenheimer, 2002 Sweden HEAVEN Study (Fair)	Dizziness Valsartan (4.3%) Enalapril (8.5%)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Dunselman, 2001 Europe REPLACE (Fair)	Heart Failure	Telmisartan 10, 20, 40, or 80mg	Enalapril 20mg	12 weeks	378
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Poor)	Heart Failure	Candesartan 4, 8, or 16mg once daily	Enalapril 10mg twice daily Candesartan 4 or 8mg once daily plus enalapril 10mg twice daily	43 weeks	768
Lang, 1997 U.S., Canada (Fair)	Heart Failure	Losartan 25mg Losartan 50mg	Enalapril 20mg	12 weeks	116
Dickstein, 1995 Scandinavia (Fair)	Heart Failure	Losartan 25mg or 50mg	Enalapril 20mg	8 weeks	166

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Dunselman, 2001 Europe REPLACE (Fair)	Telmisartan (3.1%) Enalapril (2.6%)	Cough Telmisartan (3%) Enalapril (5.6%) (P=0.3)
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Poor)	Not reported	Potassium Candesartan (-0.23±0.03 mmol/L) Enalapril (-0.01±0.05 mmol/L) (P<0.05) Candesartan + enalapril (0.11±0.03 mmol/L)(P<0.05) vs. candesartan (P<0.05) vs. candesartan
Lang, 1997 U.S., Canada (Fair)	Losartan 25mg (2.6%) Losartan 50mg (2.5%) Enalapril 20mg (2.7%)	Potassium Losartan 25mg (-0.16±0.43 mEq/L) Losartan 50mg (0.12±0.42 mEq/L) Enalapril (-0.05±0.47 mEq/L)
Dickstein, 1995 Scandinavia (Fair)	Losartan 25mg (1.9%) Losartan 50mg (3.6%) Enalapril 20mg (8.6%)	Dizziness Losartan 25mg (9.6%) Losartan 50mg (8.9%) Enalapril 20mg (6.9%) Hypotension Losartan 25mg (5.8%) Losartan 50mg (7.1%) Enalapril 20mg (6.9%)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Dunselman, 2001 Europe REPLACE (Fair)	
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Poor)	
Lang, 1997 U.S., Canada (Fair)	<u>sCr</u> Losartan 25mg (0.02+0.14 mg/dl) Losartan 50mg (0.02+0.28 mg/dl) Enalapril (0.08+0.15 mg/dl) (P<0.05 losartan 50mg vs. enalapril)
Dickstein, 1995 Scandinavia (Fair)	<u>Cough</u> Losartan 25mg (3.8%) Losartan 50mg (7.1%) Enalapril 20mg (6.9%)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	Heart Failure	Candesartan 32mg	Placebo	3.1 years	7599
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	Heart Failure	Candesartan 32mg	Placebo	3.4 years	2548

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	Candesartan (21.0%) Placebo (16.7%) (P<0.0001)	Hypotension (discontinued) Candesartan (3.5%) Placebo (1.7%) (P<0.0001) Increased sCr (discontinued) Candesartan (6.2%) Placebo (3.9%) (P<0.0001) Hyperkalemia (discontinued) Candesartan (2.2%) Placebo (0.6%) (P<0.0001)
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	Candesartan (24.2%) Placebo (18.3%) (P=0.0003)	Hypotension (discontinued) Candesartan (4.5%) Placebo (3.1%) (P=0.79) Increased sCr (discontinued) Candesartan (7.8%) Placebo (4.1%) (P=0.0001) Hyperkalemia (discontinued) Candesartan (3.4%) Placebo (0.7%) (P<0.0001)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	Angioedema Candesartan (0.13%) Placebo (0.08%) Doubling sCr Candesartan (6%) Placebo (4%) (P=0.002) Potassium > 6mmol/L Candesartan (2.0%) Placebo (1.0%) (P=0.017) (potassium increased 0.14 mmol/L with candesartan (P<0.0001) with no change in the placebo group at 6 weeks)
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	Angioedema Candesartan (0.16%) Placebo (0.24%) Doubling sCr Candesartan (7.0%) Placebo (6.0%) (P=0.5) Potassium > 6mmol/L Candesartan (3.0%) Placebo (1.0%) (P=0.089)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	Heart Failure	Candesartan 32mg	Placebo	2.8 years	2028

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	Candesartan (21.5%) Placebo (19.3%) (P=0.23)	Hypotension (discontinued) Candesartan (3.7%) Placebo (0.9%) (P<0.0001) Increased sCr (discontinued) Candesartan (6.1%) Placebo (2.7%) (P<0.0001) Hyperkalemia (discontinued) Candesartan (1.9%) Placebo (0.3%) (P=0.0005) Cough (discontinued) Candesartan (0.2%) Placebo (0.4%) (P=0.69)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	Angioedema (discontinued) Candesartan (0.1%) Placebo (0%) (P=0.05) Angioedema Candesartan (0.3%) Placebo (0%) (all in previous ACEI angioedema/anaphylaxis) Doubling sCr Candesartan (5.5%) Placebo (1.6%) (P=0.015) Potassium > 6mmol/L Candesartan (3.0%) Placebo (1.3%) (P=0.26)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	Heart Failure	Candesartan 32mg	Placebo	3.1 years	3023
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	Heart Failure	Valsartan 320mg	Placebo	1.9 years	5010

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	Candesartan (17.8%) Placebo (13.5%) (P=0.001)	Hypotension (discontinued) Candesartan (2.4%) Placebo (1.1%) (P=0.009) Increased sCr (discontinued) Candesartan (4.8%) Placebo (2.4%) (P=0.0005) Hyperkalemia (discontinued) Candesartan (1.5%) Placebo (0.6%) (P=0.029)
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	Valsartan (9.9%) Placebo (7.2%) (P<0.001)	Dizziness (discontinued) Valsartan (1.6%) Placebo (0.4%) (P<0.001) Hypotension (discontinued) Valsartan (1.3%) Placebo (0.8%) (P=0.124) Renal impairment (discontinued) Valsartan (1.1%) Placebo (0.2%) (P<0.001)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	Doubling sCr Candesartan (6%) Placebo (3%) (P=0.007) Potassium > 6.0 mmol/L Candesartan (2%) Placebo (1%) (P=0.32)
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	Mean change sCr Valsartan (increase 0.18mg/dl) Placebo (increase 0.10mg/dl) (P<0.001) Mean change serum potassium Valsartan (increase 0.12mmo/l) Placebo (decrease 0.07mmol/l) (P<0.001)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis (Fair)	Heart Failure	Valsartan 320mg	Placebo	1.9 years	366
Tonkon, 2000 U.S. (Poor)	Heart Failure	Irbesartan 150mg	Placebo	12 weeks	109

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis (Fair)	Valsartan (9.7%) Placebo (12.7%) (P=0.367)	Hypotension (discontinued) Valsartan (0.5%) Placebo (0.6%) (P=0.988) Dizziness Valsartan (23.9%) Placebo (18.9%) Hypotension Valsartan (14.7%) Placebo (5.6%)
Tonkon, 2000 U.S. (Poor)	Irbesartan (7.0%) Placebo (3.9%)	CV events (discontinued) Irbesartan (7.0%) Placebo (3.9%) Dizziness Irbesartan (23.0%) Placebo (23.0%) Hypotension Irbesartan (12.0%) Placebo (0%)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis (Fair)	Headache Irbesartan (19.0%) Placebo (12.0%) Increase sCr Valsartan (0.18+0.2mg/dl) Placebo (0.10+0.02mg/dl) (P=0.009)
Tonkon, 2000 U.S. (Poor)	Headache Irbesartan (19.0%) Placebo (12.0%) Potassium Irbesartan (0.01 mEq/L) Placebo (-0.08mEq/L) sCr Irbesartan (0.08 mg/dl) Placebo (0.04 mg/dl)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Disease	Interventions (drug, dose, duration)	Control	Duration	Number enrolled
Riegger, 1999 Europe STRETCH Trial (Fair)	Heart Failure	Candesartan 8mg, 16mg	Placebo	12 weeks	844
Hamroff, 1999 U.S., France (Fair)	Heart Failure	Losartan 50mg	Placebo	6 months	33
Warner, 1999 U.S. (Fair)	Heart Failure	Losartan 50mg	Placebo	6 weeks	21
Granger, 2000 U.S., Canada, Europe (Fair)	Heart Failure	Candesartan 16 mg	Placebo	12 weeks	270

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Withdrawals due to adverse events	Adverse Effects Reported
Riegger, 1999 Europe STRETCH Trial (Fair)	Candesartan 4mg (1.9%) Candesartan 8mg (4.7%) Candesartan 16mg (5.6%) Placebo (4.3%)	Serious adverse events Candesartan 4mg (1.4%) Candesartan 8mg (5.7%) Candesartan 16mg (5.6%) Placebo (4.7%) Possibly related to symptomatic hypotension Candesartan 4mg (1.5%) Candesartan 8mg (2.8%) Candesartan 16mg (0.5%) Placebo (1.9%)
Hamroff, 1999 U.S., France (Fair)	Losartan (6.25%) Placebo (5.9%)	Treatment reported to be well-tolerated in both groups, without adverse side effects
Warner, 1999 U.S. (Fair)	Losartan (5.0%) Placebo (0%)	Increase in sCr (discontinued therapy) Losartan (5.0%)
Granger, 2000 U.S., Canada, Europe (Fair)	Candesartan (11.7%) Placebo (8.8%)	Cough Placebo (64.8%) Candesartan (68.2%) Renal Failure Placebo (11.0%) Candesartan (11.2%)

Evidence Table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported
Riegger, 1999 Europe STRETCH Trial (Fair)	Increase in sCr Candesartan 4mg (2.9%) Candesartan 8mg (4.2%) Candesartan 16mg (0.9%) Placebo (1.9%)
Hamroff, 1999 U.S., France (Fair)	
Warner, 1999 U.S. (Fair)	
Granger, 2000 U.S., Canada, Europe (Fair)	Angioedema Placebo (4.4%) Candesartan (4.5%) Discontinuation due to renal insufficiency Placebo (3%) Candesartan (7%)

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Biswas et al 2002 England (Fair for adverse events)	Retrospective cohort	Dispensed National Health Service prescriptions written by GPs in England between December 1996 and November 1998.	Valsartan

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions
Biswas et al 2002 England (Fair for adverse events)	NA	NA

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Biswas et al 2002 England (Fair for adverse events)	Questionnaire sent to prescribing GP at least 6 months after the date of the first prescription for each individual patient. Mailed questionnaire to GP and patient. An 'event' was defined as any new diagnosis, any reason for referral to a consultant or admission to hospital, and unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, or any complaint considered to be of sufficient importance to enter into the patient's notes.	Mean age (SD) for males 61.1 (12.1); females 65.4 (12.5); age not recorded for 11.7% of patients. 40.5% male, 59% female, 0.5% not specified Ethnicity not reported

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Biswas et al 2002 England (Fair for adverse events)	Major indication for prescribing: hypertension 64.3%, cough 1.9%, not specified 29.2%.	14,127 of 25,838 (55%) forms mailed were returned.	1246 forms were void. Reasons: no longer registered with doctor (762), blank forms (246), no record of treatment in notes (166), valsartan prescribed but not taken (22), duplicate form for patient (33), patient's doctor died, moved, or retired (17). 12,881 analyzed.

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Biswas et al 2002 England (Fair for adverse events)	295 events in 209 patients (1.6% of the cohort) were reported to have been adverse reactions to valsartan. Most frequently reported adverse reaction was unspecified side effects in 57 (0.4%) patients, malaise/lassitude in 37 (0.3%) patients, and dizziness in 19 (0.1%). Two reports of drug interaction: 1 ibuprofen causing indigestion and heartburn, 1 warfarin causing "deranged INR."	Same as method of outcome assessment.	See Results	19.9% had stopped taking valsartan by 6 months (2562/14,127). Most frequent reasons for stopping treatment were "not effective" (847 reports, 6.5%), malaise/lassitude 265 reports, 2%), and dizziness (146 reports, 1.1%).

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Benz et al 1997 (Fair overall, fair for adverse events)	RCT	Male and female outpatients aged 18 to 80 years with uncomplicated essential hypertension and a history of ACE inhibitor-induced cough.	Valsartan 80mg, lisinopril 10mg, or 25 mg hydrochlorothiazide for 6 weeks.

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions
Benz et al 1997 (Fair overall, fair for adverse events)	2 to 4 weeks of single-blind placebo treatment to wash out previous antihypertensive medication and demonstrate the absence of cough and the presence of raised blood pressure, followed by 2 to 4 weeks of lisinopril challenge to confirm he presence of an ACE inhibitor-induced cough. Then a further 2 weeks of single-blind placebo treatment to confirm that the cough had resolved and to wash out the lisinopril before randomization.	No

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Benz et al 1997 (Fair overall, fair for adverse events)	Presence of a dry, persistent cough determined using a patient questionnaire at each visit after enrollment. Assessments at enrollment, before and after the lisinopril challenge, at randomization, and at 3 and 6 weeks of double-blind treatment.	Mean age 53.6 55% male 93% white, 3.1% black, 3.9% other

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Benz et al 1997 (Fair overall, fair for adverse events)	93% of valsartan group and 100% of lisinopril and hydrochlorothiazide patients had significant medical history and/or concomitant diagnosis. (statistically significant, p-value not reported)	197 screened/141 eligible/129 enrolled	23 withdrew/1 lost to followup/128 analyzed

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Benz et al 1997 (Fair overall, fair for adverse events)	Incidence of dry persistent cough after 3 or 6 weeks (combined) treatment: valsartan 19.5% lisinopril 68.9% hydrochlorothiazide 19%. Difference: Valsartan vs lisinopril 49.4%, p<0.001 valsartan vs hydrochlorothiazide 0.5% P<0.969 HCTZ vs lisinopril 49.9%, P<0.004	Details of any adverse experiences, including a worsening of an existing condition, recorded at each visit.	89 patients (69%) reported an adverse experience; majority mild to moderate in severity. Frequency of any dry cough (persistent or not): lisinopril 71.1%, valsartan 21.4%, HCTZ 19%. 4 cases of cough with lisinopril considered severe. Headache: valsartan 16.7%, HCTZ 14.3%, lisinopril 2.2% Headache considered related to trial drugs: valsartan 4.8%, HCTZ 7.1%, lisinopril 0.	Withdrawals due to adverse events: lisinopril 10 patients, valsartan 3 patients, HCTZ 2 patients. Withdrawals due to dry cough: 1 valsartan, 8 lisinopril, 0 HCTZ

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Chan et al 1997 Taiwan and Hong Kong (Poor overall, fair for adverse events)	RCT	Elderly patients with hypertension with a history of cough while taking any ACE inhibitor, free of respiratory disease and major cardiac disorders such as advanced heart failure or unstable angina, and nonsmokers for at least one year.	losartan, lisinopril, or metolazone once daily for a maximum of 10 weeks.

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions
Chan et al 1997 Taiwan and Hong Kong (Poor overall, fair for adverse events)	Lisinopril 10mg administered in a single-blind fashion for a maximum of 8 weeks to confirm presence of ACE inhibitor-induced cough, then dechallenge with placebo for 4 weeks.	No

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Chan et al 1997 Taiwan and Hong Kong (Poor overall, fair for adverse events)	Presence of cough recorded by a questionnaire administered by a trained nurse. Visual analog scale marked "I never cough" (score of 0) to "I have intolerable cough." Visits scheduled at 2-week intervals, but visits were permitted at 1-week intervals if the cough was annoying to the patient's daily life.	Mean age 73 (SD 5) 42.9% male Ethnicity not reported

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Chan et al 1997 Taiwan and Hong Kong (Poor overall, fair for adverse events)	No differences among groups in duration of hypertension, blood pressure, and body mass index. No other information on diagnoses reported.	Number screened/eligible not reported/84 enrolled	Not reported

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Chan et al 1997 Taiwan and Hong Kong (Poor overall, fair for adverse events)	Incidence of cough: 97% lisinopril, 18% losartan, 21% metolazone (P<0.001 lisinopril vs losartan). Median time to development of cough with lisinopril was 15 days. VAS score for frequency of cough: lisinopril 6.0 cm (+ 1.2), losartan 0.8 cm (+ 0.2) P<0.001 lisinopril vs losartan	Not described for events other than cough.	Other than development of cough, no other major adverse events occurred.	4 patients withdrew in lisinopril group due to intolerable cough, no other withdrawals.

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Elliot 1999 US (Poor overall, fair for adverse events)	RCT	At least 18 years old with essential hypertension. Women of childbearing potential required to be using contraception.	Initially, eprosartan 200 mg twice daily or enalapril 5 mg once daily. At 3-week intervals, dose titrated as needed to a maximum dose of 300mg eprosartan twice daily or enalapril 20mg once daily. At the end of week 12, maximum doses were supplemented with hydrochlorothiazide 12.5 mg daily.

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions
Elliot 1999 US (Poor overall, fair for adverse events)	3- to 5-week single-blind placebo run-in period, an 18-week double-blind titration period, and an 8-week maintenance period.	No

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Elliot 1999 US (Poor overall, fair for adverse events)	Pulmonary assessment (physician's examination of the chest by auscultation and percussion, if abnormal) performed at screening, at randomization, at weeks 6 and 12 of the titration phase, and at the end of the maintenance phase. Presence and character of cough assessed by the investigator regarding type, duration, severity, frequency, and probable cause of cough. Cough categorized as definite, probable, possible, or a "tickle in throat." At each visit, patients completed quality-of-life questionnaire with a five-point tolerability rating scale of frequency (never, seldom, occasional, frequent, or constant) and severity for each of 10 commonly-experienced adverse events (one of which was cough). Cough that occurred at any time during the trial was recorded as an adverse experience.	Mean age 56 (SEM 0.7) 56.5% male 86.4% white, 7.6% black, 1.1% Asian, 4.9% other

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Elliot 1999 US (Poor overall, fair for adverse events)	83% history of prior antihypertensive therapy, 56% prior ACE inhibitor therapy, 0.8% prior ACE inhibitor-associated cough, 13% current smokers.	Number screened/eligible not reported/528 enrolled	Not reported

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Elliot 1999 US (Poor overall, fair for adverse events)	Incidence of definite cough at 12 weeks: 14 (5.4%) enalapril, 4 (1.5%) eprosartan (RR 3.45, 95% CI 1.26-10.0) Incidence of definite cough at 26 weeks: 6.1% enalapril, 1.5% eprosartan (RR 1.41, 95% CI 1.89)	Not described for events other than cough.	See Results	7 enalapril, 2 eprosartan patients withdrew due to cough

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Fogari et al 2001 Italy (Fair overall, fair for adverse events)	RCT, crossover	Men aged 40-49 years with newly diagnosed hypertension, married, with never-treated essential hypertension (DBP 95 mm HG o greater and less than 110 mm Hg) without sexual dysfunction symptoms.	Carvedilol 50mg once daily or valsartan 80mg once daily for 16 weeks, then after another 4-week placebo period, crossed over to the alternative regimen.
Fogari et al 2002 Italy (Poor overall, fair for adverse events)	RCT	Men aged 40-49 years, married, with newly diagnosed, previously untreated essential hypertension (diastolic blood pressure 95 mmHg or higher and less than 110 mmgHg) and without sexual dysfunction symptoms.	Valsartan 80 mg daily or atenolol 50 mg once daily for 16 weeks. After 8 weeks the dose was doubled in the non-responders (DBP >90mmHg).

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions
Fogari et al 2001 Italy (Fair overall, fair for adverse events)	4-week placebo run-in before each treatment period.	No
Fogari et al 2002 Italy (Poor overall, fair for adverse events)	4-week placebo run-in.	No

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Fogari et al 2001 Italy (Fair overall, fair for adverse events)	At each visit, patients given a questionnaire with instructions for self-completion. Questionnaires completed by the respondent in a private area. Questions dealing with sexual function (Have you noted a decrease of interest in sex? Did you have problems in gaining an erection? Did you have problems in maintaining an erection? How many times did you have sexual intercourse in the last 2 weeks?) were part of a series of questions on various aspects of quality of life. Assessments at the screening visit (baseline) and every 4 weeks thereafter.	Mean age 46.6 100% male Ethnicity not reported
Fogari et al 2002 Italy (Poor overall, fair for adverse events)	At each visit, patients given a questionnaire with instructions for self-completion. Questionnaires completed by the respondent in a private area. Questions dealing with sexual function were part of a series of questions on various aspects of quality of life. Primary measure of treatment effect on sexual function was sexual activity assessed as mean number of sexual intercourse episodes per month. Assessments at the screening visit (baseline), at the end of the placebo period and after 8 weeks and 16 weeks of treatment.	Mean age not reported (range 40-49) 100% male Ethnicity not reported

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Fogari et al 2001 Italy (Fair overall, fair for adverse events)	Newly diagnosed, previously untreated essential hypertension. Men with erectile dysfunction were excluded from analysis.	Number screened, eligible not reported/160 enrolled	6 withdrawn/6 lost to followup/number analyzed not clear (those with erectile dysfunction not analyzed, but number not reported)
Fogari et al 2002 Italy (Poor overall, fair for adverse events)	Newly diagnosed, previously untreated essential hypertension. Men with erectile dysfunction were excluded from analysis.	Number screened, eligible not reported/110 enrolled	Not reported.

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Fogari et al 2001 Italy (Fair overall, fair for adverse events)	Decrease from baseline in episodes of sexual intercourse per month after 4 weeks of active treatment: carvedilol from 8.2 to 4.4 (-46%, P<0.01 vs baseline) valsartan from 8.3 to 6.6 (-21%, NS) Episodes of sexual intercourse per month after 16 weeks of treatment: carvedilol 3.7 + 1.4 (P<0.01 vs baseline) valsartan 10.2 + 4.6 (NS vs baseline) difference between groups P<0.01	Not described for events other than decrease in sexual activity.	Erectile dysfunction spontaneously reported: carvedilol: 15 patients (13.5%) valsartan: 1 patient (0.9%) p<0.001	6 withdrawals (1 valsartan, 1 carvedilol, 4 placebo) 2 withdrawals due to hypotension (1 valsartan, 1 carvedilol).
Fogari et al 2002 Italy (Poor overall, fair for adverse events)	Change from baseline in episodes of sexual intercourse per month after 8 weeks: atenolol: from 6.0 to 5.0 (P=0.061 vs placebo) valsartan: from 5.8 to 6.5 (P=0.053 vs atenolol) Episodes of sexual intercourse per month after 16 weeks: atenolol: 4.2 (P<0.05 vs placebo) valsartan: 7.3 (P=0.01 vs atenolol)	Not described for events other than decrease in sexual activity.	Erectile dysfunction spontaneously reported: atenolol 10 patients (18.2%) valsartan 0 patients	Not reported

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe) (Fair overall, fair for adverse events)	RCT	Men and women 21 years or older, with uncomplicated primary hypertension who had previously reported cough with an ACE inhibitor, otherwise generally healthy.	Losartan 50mg, lisinopril 20mg, or hydrochlorothiazide 25mg once daily.

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe) (Fair overall, fair for adverse events)	Patients with a history of ACE inhibitor-associated cough received lisinopril 20mg once daily in a single-blind manner for up to 6 weeks; those with moderate or more dry cough on two consecutive visits entered single-blind placebo washout period. At least 2 weeks later, patients with no dry cough on two consecutive visits were randomized to 8-week double-blind treatment period.	No

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe) (Fair overall, fair for adverse events)	Symptom Assessment Questionnaire and Visual Analogue Scale were independently completed by patients at all clinic visits before being seen by the physician or study nurse. Questionnaire assessed the severity of nine symptoms, including dry cough. Visual Analogue Scale completed to assess patient's perception of frequency of cough. Clinic visits were scheduled every 2 weeks, but patients were permitted to return earlier if indicated (i.e., if a persistent dry cough developed).	Mean age ~ 56 (SD ~ 10.5) 36% male White: 81% losartan, 98% lisinopril ($p<0.05$ vs losartan group), 88% hydrochlorothiazide Black: 10% losartan, 0 lisinopril, 7% hydrochlorothiazide Other: 8% losartan, 2% lisinopril, 4% hydrochlorothiazide

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe) (Fair overall, fair for adverse events)	No differences among groups in duration of hypertension or blood pressure. All had uncomplicated primary hypertension, otherwise generally healthy.	Number screened, eligible not reported/135 enrolled	Number withdrawn, lost to followup not reported/135 analyzed

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe) (Fair overall, fair for adverse events)	Number of patients with dry cough during 8 weeks of treatment (includes responses "a little", "moderately", "quite a bit", or "extremely") losartan 29.2% lisinopril 71.7% (P<0.01 vs other groups) HCTZ 34.1% Change in VAS from end of washout to end of treatment period (higher is more frequent cough): lisinopril 3.0 cm losartan 0.9 cm hydrochlorothiazide 1.2 cm (P<0.01 lisinopril vs losartan and HCTZ)	For events other than cough, spontaneous report.	At least one adverse event spontaneously reported: losartan 52.1%, lisinopril 63.0%, HCTZ 43.9% Drug-related adverse events: lisinopril 45.7%, losartan 22.9%, HCTZ 17.1% p<0.05 lisinopril vs losartan, <0.01 vs HCTZ	Not reported

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Lacourciere 1999 Canada (Fair overall, fair for adverse events)	RCT	Patients between ages 18 and 80 with uncomplicated mild to moderate essential hypertension and a history of ACE inhibitor-related dry cough.	Telmisartan 80 mg, lisinopril 20 mg for up to 8 weeks.

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions
Lacourciere 1999 Canada (Fair overall, fair for adverse events)	7-day screening period; challenge period of up to 6 weeks, during which the patients received single-blind, double dummy lisinopril, a 4-week washout period, double-blind treatment period of up to 8 weeks, and a 1-week, post-treatment placebo period.	Permitted paracetamol 2g per day or less and aspirin not exceeding 325 mg per day for prophylaxis of coronary artery disease.

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Lacourciere 1999 Canada (Fair overall, fair for adverse events)	Assessment for presence of cough performed using a Symptom Assessment Questionnaire and a Visual Analogue Scale independently completed by patients at all visits. SAQ evaluated incidence and severity of 9 symptoms: dry cough, dry mouth, leg cramps, racing heart, heartburn, headache, sore throat, nocturnal urination, and facial flushing. Severity of these indicated on 5-point scale ranging from "not at all" to "extremely." Visual Analogue Scale assessed frequency of symptoms appearing on the SAQ, ranging from "I never have the symptom" to " I have the symptom constantly." Frequency of cough measured at the end of the lisinopril challenge period, end of placebo and washout phase. "Time to positive" response for the development of cough during the double-blind period was also analyzed.	8% age 31-40, 60.2% age 41-64, 31.8% age 65 or older 38.6% male, 61.4% female 89.8% white (other ethnicities not reported).

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Lacourciere 1999 Canada (Fair overall, fair for adverse events)	Median duration of hypertensive disease 10.6 years for placebo, 9.3 years for telmisartan, and 6.5 years for lisinopril.	216 screened/135 eligible/92 enrolled	4 withdrawn/0 lost to followup/88 analyzed

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Lacourciere 1999 Canada (Fair overall, fair for adverse events)	Occurrence of dry cough during 8 weeks of treatment: telmisartan15.6% (P=0.004 vs lisinopril) lisinopril 60% placebo 9.7% (P=0.001 vs lisinopril) Frequency of dry cough on VAS at 8 weeks of treatment (higher is more frequent cough): telmisartan 0.83 cm (P=0.0016 vs lisinopril) lisinopril: 2.87 cm placebo: 0.92 cm (P=0.0028 vs lisinopril)	Other than cough, monitored by physical examinations, ECG, laboratory tests, and patient adverse events reporting.	Adverse events reported: 66.7% placebo patients, 53.1% telmisartan patients, 44.4% lisinopril patients. Except for cough, most were mild to moderate in intensity and not considered treatment-related.	Of those entering double-blind treatment period (n=92): 4 withdrew. 3 discontinued due to adverse events (groups not specified)

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Paster et al 1998 US (Fair overall, fair for adverse events)	RCT	Generally healthy men and women, of legal age, with hypertension and a history of ACE inhibitor-induced cough.	Losartan 50mg once daily, lisinopril 20mg once daily, or placebo for up to 8 weeks.

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions
Paster et al 1998 US (Fair overall, fair for adverse events)	Open-label lisinopril 20mg once daily for a maximum of 6 weeks as a challenge to reproduce the dry cough. Those with dry cough on two consecutive visits proceeded to 4-week, placebo washout, during which total disappearance of cough had to be documented on two consecutive visits. Those who met criteria for first 2 phases were randomly allocated to 8 weeks double-blind therapy.	No

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Paster et al 1998 US (Fair overall, fair for adverse events)	Incidence and severity of dry cough assessed at each visit using the SAQ, which listed nine symptoms (dry mouth, cramps in legs, dry cough, racing heart, heartburn, headache, sore throat, getting up at night to pass urine, and flushing face). Primary efficacy question was dry cough. Patients marked whether they had experienced the symptom in the previous week and, if so, the extent to which it had bothered them (not at all, a little, moderately, quite a bit, or extremely). Patients also used a VAS at each visit to quantify their perception of cough frequency, ranging from "I never cough" to "I am constantly coughing." Clinic visits scheduled every 2 weeks through out all phases of the trial but could be scheduled more frequently if clinically indicated (i.e., if a patient developed persistent dry cough).	Mean age 57.1 (range 31-83) 49% male 90% white, 3% Asian, 5% black, 2% other

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Paster et al 1998 US (Fair overall, fair for adverse events)	Mean duration of hypertension 10 years (range 0.3-40 years)	Number screened, eligible not reported/100 enrolled	8 withdrawn/2 lost to followup/97 analyzed

Evidence Table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Paster et al 1998 US (Fair overall, fair for adverse events)	Incidence of dry cough during 8 weeks of treatment: losartan 36.7% lisinopril 87.5% (P< 0.001 compared with losartan and placebo) placebo 31.4%	At each visit, patients were asked a non-leading question concerning how they had felt since the last visit. Physician investigator assessed whether any adverse experiences were related to therapy. Investigators masked to treatment.	No serious clinical or laboratory adverse events. 11/31 (35.5%) losartan patients, 11/34 (32.4%) lisinopril patients, and 20/35 (57.1%) placebo patients reported at least one clinical adverse event. Adverse events judged to be drug related in 2 losartan (6.5%) vs 5 lisinopril (14.7%) and 9 placebo (25.7%).	Withdrawals due to adverse events1 lisinopril (cough), 0 losartan, 5 placebo.

Quality Table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

		Internal Validity				
Author, Year Country		Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?
Tedesco, 1999 Country not stated		Method not reported	Method not reported	Yes	Yes	Yes, but method not described
Dahlof, 1997 Sweden, Australia, Finland		Method not reported	Method not reported	Yes	Yes	Not reported
Tanser, 1998 Australia, Canada, Europe, Mexico		Not reported	Not reported	Yes	Yes	Yes, but method not described
Rake, 2001 U.S.		Not reported	Not reported	Yes	Yes	Yes
Breeze, 2001 North America, Europe, South Africa		Not reported	Not reported	Yes	Yes	Yes
De Rosa, 2002	Italy	Not reported	Not reported	Yes	Yes	Yes, but method not described

Quality Table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?
Tedesco, 1999 Country not stated	Yes, but method not described	Yes, but method not described	Yes/No/No/No	No
Dahlof, 1997 Sweden, Australia, Finland	Yes	Yes, but method not described	Yes/No/No/No	No
Tanser, 1998 Australia, Canada, Europe, Mexico	Yes, but method not described	Yes, but method not described	No/No/No/No	No
Rake, 2001 U.S.	Yes	Yes	No/No/No/No	Not reported
Breeze, 2001 North America, Europe, South Africa	Yes	Yes	Yes/No/No/No	No
De Rosa, 2002 Italy	Yes, but method not described	Yes, but method not described	Yes/No/No/No	No

Quality Table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

				External Validity	
Author, Year Country		Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating	Number screened/eligible/enrolled
Tedesco, 1999 Country not stated		Yes	Unable to determine	Fair	Number screened not reported/number eligible not reported/69 enrolled
Dahlof, 1997 Sweden, Australia, Finland		Yes	Unable to determine	Fair	Number screened not reported/number eligible not reported/898 enrolled
Tanser, 1998 Australia, Canada, Europe, Mexico		No (2 patients excluded due to not having post-randomization assessments of cough)	Yes (2)	Fair	Number screened not reported/301 eligible/156 enrolled
Rake, 2001 U.S.		No (4 had insufficient information to analyze QOL)	Yes (4)	Fair	231 screened/number eligible not reported/136 enrolled
Breeze, 2001 North America, Europe, South Africa		No, different numbers of patients excluded from cough and QOL assessments	Yes (6 due to lack of baseline and/or endpoint questionnaires)	Fair	Number screened not reported/number eligible not reported/529 enrolled
De Rosa, 2002	Italy	No	No	Fair	Number screened not reported/number eligible not reported/50 enrolled

Quality Table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only?
Tedesco, 1999 Country not stated	Recent MI or stroke, renal failure, chronic severe liver disease, congestive HF	Yes	Not reported
Dahlof, 1997 Sweden, Australia, Finland	Women of child-bearing age, significant renal impairment, MI within previous 6 months, angina, congestive HF, beta-blockers and other antihypertensive agents, previous AIIRA or CCB	Yes	Yes
Tanser, 1998 Australia, Canada, Europe, Mexico	Obstructive pulmonary disease; smoking; concomitant medication including NSAIDs; aspirin; codeine; antitussive agents; secondary or malignant hypertension; sitting DBP > 105 mm Hg or SBP > 180 mm Hg; severe cardiovascular liver, renal, or allergic disease, renal artery stenosis or transplantation, past or present drug abuse, childbearing potential, or hypersensitivity to study drugs	Yes	No
Rake, 2001 U.S.	Not reported	Yes	No
Breeze, 2001 North America, Europe, South Africa	Not reported	Yes	No
De Rosa, 2002 Italy	Significant cardiovascular, cerebrovascular, renal or hepatic disease, recent MI and secondary HTN	Yes	No

Quality Table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Control group standard of care?	Funding	Relevance?
Tedesco, 1999 Country not stated	Yes	Not reported	Yes
Dahlof, 1997 Sweden, Australia, Finland	Yes	Financial support by Merck & Co., Inc. (coordination efforts of sponsor employee acknowledged)	Yes
Tanser, 1998 Australia, Canada, Europe, Mexico	Yes	Supported by a grant from Astra Hassle	Yes
Rake, 2001 U.S.	Yes	Funded by SmithKline Beecham Pharmaceutical Inc	Yes
Breeze, 2001 North America, Europe, South Africa	Yes	Funded by SmithKline Beecham Pharmaceutical Inc	Yes
De Rosa, 2002 Italy	Yes	Not reported	Yes

Quality Table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Internal Validity Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?
Lithell, 2003 U.S., Canada, Europe SCOPE trial	Yes	Yes	Yes	Yes	No
Parving, 2001 Canada, Europe, South America, South Africa	Not reported	Not reported	Yes	Yes	Yes, but method not described

Quality Table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?
Lithell, 2003 U.S., Canada, Europe SCOPE trial	Yes	Yes	Yes/No/No/Yes	No
Parving, 2001 Canada, Europe, South America, South Africa	Yes, but method not described	Yes, but method not described	Yes/No/Yes/No	No

Quality Table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Lithell, 2003 U.S., Canada, Europe SCOPE trial	Yes (although 13 excluded post-randomization for data quality concerns)	Yes (27 total: 13 data quality concerns; 14 no study drug dispensed)	Fair
Parving, 2001 Canada, Europe, South America, South Africa	Yes	No	Fair

Quality Table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Lithell, 2003 U.S., Canada, Europe SCOPE trial	Number screened not reported/4964 randomized/4937 enrolled	Secondary HTN, SBP ≥ 180 mm Hg, orthostatic hypotension, need for treatment with other than HCTZ during run-in, MI or stroke within previous 6 months, decompensated HF, AST or ALT > 3 times upper limit normal, sCr > 180umol/l (men) and > 140 umol/l (women), contraindications to study drug or HCTZ, serious concomitant diseases affecting survival, alcohol or drug abuse; dementia, treatment with drugs for dementia, conditions that preclude MMSE, vitamin B12 deficiency or hypothyroidism treated < 12 months, neurosyphilis or AIDS, severe brain disorder, certain mental disorders, psychopharmacologic therapy started with previous 6 months
Parving, 2001 Canada, Europe, South America, South Africa	Number screened not reported/1469 eligible/611 enrolled	Nondiabetic kidney disease, cancer, life-threatening disease with death expected to occur within two years, and an indication for angiotension-converting-enzyme (ACE) inhibitors or angiotensin II receptor antagonists

Quality Table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Lithell, 2003 U.S., Canada, Europe SCOPE trial	Yes	Not reported	Yes	Financially supported by AstraZeneca (data entered into sponsor's database, employees of sponsor were non-voting members of the Executive and Steering Committees)	Yes
Parving, 2001 Canada, Europe, South America, South Africa	3-week run-in screening period during which all antihypertensive treatment was discontinued and replaced by placebo	No	Yes	Supported by a grant from Sanofi-Synthlabo and Bristol-Myers Squibb	Yes

Quality Table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Internal Validity: Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial	Method not reported	Method not reported	Yes	Yes	Yes
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease)	Method not reported	Method not reported	Yes	Yes	Yes
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH)	Method not reported	Method not reported	Yes	Yes	Yes
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM)	Method not reported	Method not reported	Yes	Yes	Yes

Quality Table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial	Yes, but method not described	Yes, but method not described	Yes/No/No/No	No
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease)	Yes, but method not described	Yes, but method not described	Yes/No/No/No	No
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH)	Yes, but method not described	Yes, but method not described	Yes/No/No/No	No
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM)	Yes, but method not described	Yes, but method not described	Yes/No/No/Yes	No

Quality Table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating	External Validity Number screened/eligible/enrolled
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial	Yes	No	Good	10,780 screened/9222 eligible/9193 enrolled
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease)	Yes	Unable to determine	Good	10,780 screened/9222 eligible/6886 of 9193 enrolled in substudy
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH)	Yes	No	Good	10,780 screened/9222 eligible/1326 of 9193 enrolled in substudy
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM)	Yes	No	Good	10,780 screened/9222 eligible/1195 of 9193 enrolled in substudy

Quality Table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only?
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial	Secondary HTN, MI or stroke within previous 6 months, angina requiring beta-blockers or CCBs, HF or LVEF ≤ 40%, any disorder requiring treatment with an AIIRA, beta-blocker, HCTZ, or ACEI	Yes	Not reported
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease)	Secondary HTN, MI or stroke within previous 6 months, angina requiring beta-blockers or CCBs, HF or LVEF ≤ 40%, any disorder requiring treatment with an AIIRA, beta-blocker, HCTZ, or ACEI	Yes	Not reported
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH)	Clinical evidence of vascular disease, secondary HTN, MI or stroke within previous 6 months, angina requiring beta-blockers or CCBs, HF or LVEF ≤ 40%, any disorder requiring treatment with an AIIRA, beta-blocker, HCTZ, or ACEI	Yes	Not reported
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM)	Clinical evidence of vascular disease, secondary HTN, MI or stroke within previous 6 months, angina requiring beta-blockers or CCBs, HF or LVEF ≤ 40%, any disorder requiring treatment with an AIIRA, beta-blocker, HCTZ, or ACEI	Yes	Not reported

Quality Table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Control group standard of care?	Funding	Relevance?
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial	Yes	Supported by an unrestricted grant from Merck (steering committee had free access to study data in sponsor's database to interpret data and write the manuscript)	Yes
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease)	Yes	Supported by a grant from Merck & Co. (helped refine study, provided data management assistance and data collection, and performed statistical analyses)	Yes
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH)	Yes	Supported by an unrestricted grant from Merck & Co. (reviewed manuscript)	Yes
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM)	Yes	Supported by an unrestricted grant from Merck (study data in sponsors database, free access by steering committee; reviewed manuscript)	Yes

Quality Table 4. Head-to-head trials of angiotensin II receptor antagonists in patients after recent myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both (N=2)

	Internal Validity			
Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial	Yes	Yes	Yes (note:data missing on similar number of patients for LVEF, Killip class, and site and type of MI)	Yes
Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAAL trial	Yes	Yes	Yes	Yes

Quality Table 4. Head-to-head trials of angiotensin II receptor antagonists in patients after recent myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both (N=2)

Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat analysis?
Yes	Yes	Yes	Yes/No/Yes/Yes	No	Yes
Yes	Yes	Yes	Yes/No/Yes/No	No	Yes

Quality Table 4. Head-to-head trials of angiotensin II receptor antagonists in patients after recent myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both (N=2)

		External Validity
Post-randomization exclusions?	**Quality Rating**	**Number screened/eligible/enrolled**
Yes (105 at one site due to potential inadequate informed consent process)	Good	Number screened not reported/number eligible not reported/14,808 enrolled (14,703 analyzed as 105 from one site were censored prior to unblinding)
No	Good	31,738 screened/number eligible not reported/5477 enrolled

Quality Table 4. Head-to-head trials of angiotensin II receptor antagonists in patients after recent myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both (N=2)

Exclusion criteria	Run-in/Washout	Class naïve patients only?	Control group standard of care?
Previous intolerance or contraindication to ACEI or AIIRA, clinically significant valvular disease, any disease known to severely limit life expectancy, written informed consent not available	None	No	Yes
Supine SBP < 100 mm Hg, current treatment with ACEI or AIIRA, unstable angina, hemodynamically significant stenotic valvular disease or dysrhythmia, and planned coronary revascularization	None	Yes (at time of enrollment)	Yes

Quality Table 4. Head-to-head trials of angiotensin II receptor antagonists in patients after recent myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both (N=2)

Funding	Relevance?
Supported by a grant from Novartis Pharmaceuticals (sponsor verified all analyses and reviewed manuscript)	Yes
Supported by an unconditional grant from Merck, Sharp and Dohme Research Laboratories (sponsor provided assistance in data management and included 2 non-voting members on the steering committee)	Yes

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	Internal Validity			
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial	Yes	Yes	Yes	Yes
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial	Method not reported	Method not reported	Yes	Yes
Houghton, 1999 U.K. ELITE Trial substudy	Method not reported	Method not reported	Yes	Yes

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial	Yes	Yes	Yes	Yes/No/No/Yes
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial	Yes	Yes	Yes	Yes/No/No/No
Houghton, 1999 U.K. ELITE Trial substudy	Yes	Yes	Yes	Yes/No/No/No

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial	No	Yes	No	Good
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial	Not reported	Yes	No	Fair
Houghton, 1999 U.K. ELITE Trial substudy	No	Yes	Unable to determine	Fair

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial	Number screened not reported/number eligible not reported/3152 enrolled	Previous intolerance to ACEIs or AIIRAs, SBP < 90 mm Hg, DBP > 95 mm Hg, hemodynamically important stenotic valvular heart disease, acute myocarditis or pericarditis, automatic implanted cardioverter defibrillators, coronary angioplasty within 1 week of enrollment, CABG, AMI or unstable angina within 2 weeks of enrollment, CVA or TIA within 6 weeks of enrollment, documented or significant renal artery stenosis, hematuria, sCr > 220 umol/L
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial	Number screened not reported/number eligible not reported/722 enrolled	SBP < 90 mm Hg or uncontrolled HTN (DBP > 95 mm Hg), significant obstructive valvular disease or symptomatic ventricular or supraventricular arrhythmia, constrictive pericarditis or acute myocarditis, cardiac surgery likely during study period or angioplasty within previous 72hrs, CABG or ICD within 2 weeks, AMI in previous 72hrs, unstable angina within 3 months, or angina (requiring 5 NTG tabs/wk) within 6 weeks, stroke or TIA in previous 3 months, digitalis toxicity, uncontrolled DM, chronic cough or angioedema of any etiology, untreated thyrotoxicosis or hypothyroidism, renal artery stenosis, contraindication to a vasodilator, unlikely survival for length of study or risk to patient, previous treatment with an AIIRA, sCr $\geq$ 221 umol/L (2.5mg/dl), potassium < 3.5 or > 5.5 mmol/L, potential for noncompliance
Houghton, 1999 U.K. ELITE Trial substudy	Number screened not reported/number eligible not reported/18 enrolled	same exclusion criteria as in ELITE (see above)

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial	Yes	Yes (unless length of therapy < 7 days within 3 months prior to randomization)	No (only 22% treated with beta-blockers)	Funded by Merck Research Laboratories (sponsor involved in study design, conduct of the study, statistical analyses, and writing the paper)	No
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial	Yes	Yes	No (only 16% treated with beta-blockers)	Funded by Merck Research Laboratories (sponsor involved in directing and coordinating study, statistical analyses and data coordination, and writing the paper)	No
Houghton, 1999 U.K. ELITE Trial substudy	Yes	Yes	No (none treated with beta-blockers)	Funded by Merck Sharp and Dohme Ltd (role of sponsor not specified)	No

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	Internal Validity			
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**
Cowley, 2000 U.S. ELITE Trial QOL substudy	Method not reported	Yes	Yes	Yes
Willenheimer, 2002 Sweden HEAVEN Study	Method not reported	Method not reported	Yes	Yes
Dunselman, 2001 Europe REPLACE	Method not reported	Method not reported	Yes	Yes
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD	Method not reported	Method not reported	No	Yes

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Cowley, 2000 U.S. ELITE Trial QOL substudy	Yes	Yes	Yes	Yes/No/No/No
Willenheimer, 2002 Sweden HEAVEN Study	Not reported	Yes, but method not described	Yes, but method not described	Yes/No/No/No
Dunselman, 2001 Europe REPLACE	Not reported	Yes, but method not described	Yes, but method not described	Yes/No/No/No
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD	Not reported	Yes	Yes	No/No/Yes/No

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Cowley, 2000 U.S. ELITE Trial QOL substudy	No	No	Yes (QOL data unavailable:10 losartan; 12 captopril)	Fair
Willenheimer, 2002 Sweden HEAVEN Study	No	ITT for primary endpoint; per protocol population	Yes (7 patients; reason not listed)	Fair
Dunselman, 2001 Europe REPLACE	No	No	No	Fair
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD	Not reported	No	Yes (1 for protocol violation)	Poor

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Cowley, 2000 U.S. ELITE Trial QOL substudy	Number screened not reported/300 eligible/278 enrolled	same exclusion criteria as in ELITE (see above)
Willenheimer, 2002 Sweden HEAVEN Study	Number screened not reported/146 enrolled/141 randomized	Hemodynamically significant primary valvular disease, HF due to pulmonary disease, infective cardiomyopathy, MI or coronary intervention with 3 months, unstable coronary disease, severe arrhythmia, recent stroke, sCr $\geq$ 200 umol/L or other significant laboratory abnormality, AIIRA treatment within previous 3 months, persistent standing SBP < 90 mm Hg, and at investigators discretion
Dunselman, 2001 Europe REPLACE	Number screened not reported/number eligible not reported/378 enrolled	Any life-threatening disease (e.g., cancer, hemodynamically significant pulmonary embolism, AIDS), clinically significant stenotic valvular disease, aortic or mitral regurgitation, or hypertrophic or restrictive cardiomyopathy, history of MI, unstable angina, syncopal episodes, or surgery within previous 6 months, fever, primary renal, hepatic, or metabolic disease, treatment with PDE5 inhibitors, dopamine or beta-agonists, class I antiarrhythmic agents, chronic administration of high doses of NSAIDs or acetaminophen, women of child-bearing potential, treatment with telmisartan or other investigational drug within previous 4 weeks
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD	Number screened not reported/899 eligible/768 enrolled	Acutely ill, renal impairment, contraindications to study medications

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Cowley, 2000 U.S. ELITE Trial QOL substudy	Yes	Yes	No (based on ELITE)	Funded by Merck Research Laboratories (sponsor includes 4 of first 7 authors on the paper)	No (based on ELITE)
Willenheimer, 2002 Sweden HEAVEN Study	Yes	No	Yes	Funded by a grant from Novartis Pharma (role of sponsor not specified)	Yes
Dunselman, 2001 Europe REPLACE	Yes	No	Yes	Funded by Boehringer-Ingelheim Limited (role of sponsor not specified)	Yes
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD	Yes	No	No (only 15% treated with beta-blockers during initial 19 weeks of study)	Supported by a grant from Astra (role of sponsor not specified)	No

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	Internal Validity			
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**
Lang, 1997 U.S., Canada	Method not reported	Method not reported	No	Yes
Dickstein, 1995 Scandinavia	Method not reported	Method not reported	Yes	Yes

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Lang, 1997 U.S., Canada	Not reported	Yes, but method not described	Yes, but method not described	No/No/No/No
Dickstein, 1995 Scandinavia	Not reported	Yes	Yes	Yes/No/No/No

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Lang, 1997 U.S., Canada	Not reported	No	Unable to determine	Fair
Dickstein, 1995 Scandinavia	Not reported	No	No	Fair

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Lang, 1997 U.S., Canada	Number screened not reported/number eligible not reported/116 enrolled	Not reported
Dickstein, 1995 Scandinavia	Number screened not reported/number eligible not reported/166 enrolled	Not reported

Quality Table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Lang, 1997 U.S., Canada	Yes	No	No (only 7% treated with beta-blockers)	Supported by a grant from Merck Research Laboratories (role of sponsor not specified; sponsor included as 3 of primary authors on paper)	No
Dickstein, 1995 Scandinavia	Yes	No	No (only 12% treated with beta-blockers)	Supported by a grant from Merck, Sharp and Dohme Research Laboratories (role of sponsor not specified; sponsor included as 1 of primary authors on paper)	No

Quality Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Internal Validity: Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial	Yes	Yes	Not reported	Yes
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial	Yes	Yes	Not reported	Yes
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial	Yes	Yes	Not reported	Yes
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial	Yes	Yes	Yes	Yes
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial	Yes	Yes	Yes	Yes
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis	Yes	Yes	Yes (except greater percent with NYHA class III-IV in placebo vs. valsartan, P<0.05)	Yes

Quality Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial	Yes	Yes	Yes	Yes/No/No/No
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial	Yes	Yes	Yes	Yes/No/No/Yes
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial	Yes	Yes	Yes	Yes/No/No/Yes
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial	Yes	Yes	Yes	Yes/No/No/Yes
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial	Yes	Yes	Yes	No/No/No/No
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis	Yes	Yes	Yes	Yes/No/No/No

Quality Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	oss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial	No	Yes	Yes (2 patients without data)	Good
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial	No	Yes	No	Good
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial	No	Yes	No	Good
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial	No	Yes	Yes (2 patients without data - see Overall study)	Good
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial	Not reported	Yes	No	Good
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis	Not reported	Yes	Unable to determine	Fair

Quality Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

	External Validity	
Author, Year Country	Number screened/eligible/enrolled	Exclusion criteria
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial	Number screened not reported/7601 eligible/7599 enrolled	Bilateral renal artery stenosis, symptomatic hypotension, MI, stroke, or open-heart surgery in previous 4 weeks, critical aortic or mitral stenosis, non-cardiac disease that may limit 2-year survival, sCr > 265 *u* mol/L, serum potassium > 5.5mmol/L, women of child-bearing potential not on adequate contraception, use of an AIIRA in previous 2 weeks, unwilling to consent
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial	Number screened not reported/number eligible not reported/2548 enrolled	Not reported
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial	Number screened not reported/number eligible not reported/2028 enrolled	Not reported
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial	Number screened not reported/3025 eligible/3023 enrolled	Not reported
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial	Number screened not reported/number eligible not reported/5010 enrolled	Currently on AIIRA
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis	Number screened not reported/number eligible not reported/5010 enrolled in Val-HeFT/366 not treated with ACEI in substudy	Not treated with ACEI

Quality Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial	No	No	Yes	Supported by AstraZeneca (sponsor managed data, involved in statistical analysis, data interpretation)	Yes
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial	No	No	Yes	Supported by AstraZeneca (sponsor managed data, involved in statistical analysis, data interpretation)	Yes
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial	No	No	Yes	Supported by AstraZeneca (sponsor managed data, involved in statistical analysis, data interpretation)	Yes
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial	No	No	Yes	Supported by AstraZeneca (sponsor managed data, involved in statistical analysis, data interpretation)	Yes
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial	Yes	No	Yes	Supported by a grant from Novartis Pharmaceuticals (sponsor involved in site monitoring, data collection, data analysis)	Yes
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis	Yes	No	Yes	Funding provided by Novartis Pharma (role of sponsor in substudy not specified)	Yes

Quality Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Internal Validity: Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Tonkon, 2000 U.S.	Method not reported	Method not reported	No (open-label ACEI doses inconsistent)	Yes
Riegger, 1999 Europe STRETCH Trial	Yes	Yes	Yes	Yes
Hamroff, 1999 U.S., France	Method not reported	Method not reported	No (higher percent of males in placebo group; mean daily dose captopril higher in losartan group)	Yes
Warner, 1999 U.S.	Method not reported	Method not reported	Not reported	Yes
Granger, 2000 U.S., Canada, Europe	Not reported	Not reported	No NYHA Class II Placebo=47.3% Candesartan=57% NYHA Class III Placebo=49.5% Candesartan=36.3%	Yes

Quality Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Tonkon, 2000 U.S.	Not reported	Yes, but method not described	Yes, but method not described	Yes/No/No/No
Riegger, 1999 Europe STRETCH Trial	Not reported	Yes	Yes	Yes/No/No/Yes
Hamroff, 1999 U.S., France	Not reported	Yes, but method not described	Yes, but method not described	Yes/No/No/No
Warner, 1999 U.S.	Not reported	Yes	Yes	Yes/No/No/No
Granger, 2000 U.S., Canada, Europe	Yes, but method not described	Yes, but method not described	Yes, but method not described	Yes/No/No/No

Quality Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	oss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Tonkon, 2000 U.S.	Not reported	No	Yes (5 required concomitant medications that were not allowed or patients failed to meet protocol requirements; 6 due to adverse events; 1 voluntarily withdrew)	Poor
Riegger, 1999 Europe STRETCH Trial	No	Yes	Yes (55 total: 29 adverse events; 11 patient's request; 8 exclusion critera; 1 noncompliance; 6 unspecified)	Fair
Hamroff, 1999 U.S., France	No	No	Unable to determine	Fair
Warner, 1999 U.S.	No	No	Yes (1 had increase sCr 1.5 to 2.0mg/dl)	Fair
Granger, 2000 U.S., Canada, Europe	No	Yes	No	Fair

Quality Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

	External Validity	
Author, Year Country	Number screened/eligible/enrolled	Exclusion criteria
Tonkon, 2000 U.S.	Number screened not reported/145 enrolled/109 randomized	Concomitant medication or disease causing risk to patient or interfere with study goals
Riegger, 1999 Europe STRETCH Trial	Number screened not reported/926 enrolled/844 randomized	Severe or malignant HTN, symptomatic hypotension, MI within 3 months, hemodynamically relevant arrhythmias, pacemakers or implanted cardioverters, hemodynamically relevant valvular defect or insufficiency, angina, clinically significant disease, autoimmune or wasting disease, psychological illness, drug or alcohol addiction, type 1 DM, uncontrolled DM or requiring insulin, limitation of exercise capacity for reason other than HF, pregnant or lactating wormen, patients unwilling to comply with study protocol or in another clinical trial within 1 month, treatment with concomitant beta-blockers, antihypertensives, other agents causing systemic vasodilation or vasoconstriction, NSAIDs, antiarrhythmics, immunosuppressive or cytotoxic agents, insulin, or any drug altering GI absorption
Hamroff, 1999 U.S., France	Number screened not reported/number eligible not reported/33 enrolled	Not reported
Warner, 1999 U.S.	Number screened not reported/number eligible not reported/21 enrolled	MI on stress echocardiogram, valvular heart disease, other disease that could limit exercise tolerance, previous AIIRA use
Granger, 2000 U.S., Canada, Europe	Number screened not reported/288 eligible/270 enrolled	ACE inhibitor use; creatinine level of 220 umol/L or more; potassium level more than 5.5 mmol/L; history of serious hyperkalemia induced by use of an ACE inhibitor; use of potassium-sparing diuretics; known renal arterial stenosis; renal transplantation; use of angiotensin receptor blocker or any investigational drug within 30 days; pregnancy; poor compliance; uncontrolled hypertension; unstable angina; acute myocardial infarction; percutaneous coronary angioplasty or coronary artery bypass operation within 30 days; stroke or transient ischemic attack within 3 months; obstructive valvular heart disease; constrictive pericarditis; or any noncardiac illness that limited expected survival to less than 2 years

Quality Table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Tonkon, 2000 U.S.	Yes	No	No (beta-blockers withdrawn)	Funding source not listed (2 primary authors, one of which is the corresponding author, from Bristol-Myers Squibb Pharmaceutical Research Institute)	No
Riegger, 1999 Europe STRETCH Trial	Yes	Not reported	No (beta-blockers not allowed)	Funding source not listed (2 primary authors from Takeda Europe R&D)	No
Hamroff, 1999 U.S., France	Yes	Not reported	No (only 6% on beta-blockers)	No funding source listed	No
Warner, 1999 U.S.	Yes	Yes	Yes	Supported in part by a research grant from NIH and Merck Research Laboratories	Yes
Granger, 2000 U.S., Canada, Europe	Yes	No	Yes	Supported by a grant from Astra Hassle (included as authors of paper)	Yes

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Internal Validity: Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Nakao, 2003 Japan COOPERATE	Yes	Yes	Yes	Yes
Lacourciere, 2000 Canada	Not reported	Not reported	No SIDBP Losartan 97.2 mm Hg Enalapril 95.3 mm Hg (P=0.025) Mean diabetes duration (years) Losartan 9.2 Enalapril 12.6 (P=0.039)	Yes
Luno, 2002 Spain	Yes	Not reported	Yes	Yes

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Internal Validity: Outcome assessors masked?	Internal Validity: Care provider masked?	Internal Validity: Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Nakao, 2003 Japan COOPERATE	Yes	Yes	Yes	Yes/No/No/No
Lacourciere, 2000 Canada	Yes, but method not described	Yes, but method not described	Yes, but method not described	Yes/No/No/No
Luno, 2002 Spain	Open	Open	Open	Yes/No/No/No

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Nakao, 2003 Japan COOPERATE	No	Yes	No	Good
Lacourciere, 2000 Canada	No	No	No	Poor
Luno, 2002 Spain	No	Yes	No	Fair

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	External Validity Number screened/eligible/enrolled	External Validity Exclusion criteria
Nakao, 2003 Japan COOPERATE	336 screened/306 eligible/263 enrolled	Need for immediate renal replacement therapy; resistant edema; treatment with corticosteroids, NSAIDs, or immunosuppressive drugs; proteinuria > 10g/d and hypoalbuminemia < 28g/L; renovascular HTN; malignant HTN; MI, or stroke in previous year; severe PVD; severe CHF (NYHA class III-IV); chronic hepatic disease; connective tissue disease; obstructive uropathy; cancer; COPD; drug or alcohol misuse; pregnancy; breastfeeding
Lacourciere, 2000 Canada	Number screened not reported/number eligible not reported/103 enrolled	Evidence or suspicion of renovascular disease; history of malignant HTN; SBP > 210 mm Hg; CVA in the previous 12 months or current transient ischemic attacks; MI within the previous 12 months; clinically significant arteriovenous (AV) conduction disturbances and/or arrhythmias; unstable angina; history of HF; sCr ≥ 200 mmol/L; serum potassium ≥ 5.5 mmol/L or ≤ 3.5 mmol/L; treatment with oral corticosteroids; concomitant use of agents that may affect BP except beta blockers and nitrates used in the treatment of stable angina; drug or alcohol abuse; pregnancy; breast feeding; ineffective contraception
Luno, 2002 Spain	Number screened not reported/number eligible not reported/46 enrolled	Nephrotic patients with serum albumin <3.0 g/dL as well as those with hypertension stage 3 (SBP≥180 mm Hg and/or DBP ≥110 mm Hg), hyperkalemia (>5.0 mmol/L), secondary glomerular diseases, systemic diseases (diabetes mellitus, amyloidosis, systemic lupus erythematosus), or those with any severe cardiovascular even in the last 3 months before randomization; severe cardiac, pulmonary or hepatic disease, HIV infection and neoplasia; corticosteroid and/or immunosuppressive therapy use within six months

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?
Nakao, 2003 Japan COOPERATE	Yes	No	Yes
Lacourciere, 2000 Canada	Yes	No	Yes
Luno, 2002 Spain	Yes	No	Yes

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Funding	Relevance?
Nakao, 2003 Japan COOPERATE	Partly funded by a grant from the Progressive Renal Disease Research Projects from the Ministry of Health, Labor, and Welfare in Japan. No other funding source noted	Yes
Lacourciere, 2000 Canada	Supported by a grant from Merck	Yes
Luno, 2002 Spain	Supported by a grant from Astra Zeneca	Yes

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Internal Validity: Randomization adequate?	Internal Validity: Allocation concealment adequate?	Internal Validity: Groups similar at baseline?	Internal Validity: Eligibility criteria specified?
Muirhead, 1999 Canada	Not reported	Not reported	Yes	Yes
Andersen, 2000 Denmark	Method not reported	Method not reported	Cross-over trial	Yes
Campbell, 2003 Italy	Method not reported	Not reported	Cross-over trial	Yes

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Internal Validity			
	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Muirhead, 1999 Canada	Yes	Yes	Yes	Yes/No/No/No
Andersen, 2000 Denmark	Not reported	Yes, but method not described	Yes, but method not described	Yes/No/No/No
Campbell, 2003 Italy	Open	Open	Open	Yes/No/No/No

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Muirhead, 1999 Canada	No	No	No	Fair
Andersen, 2000 Denmark	No	Yes	Unable to determine	Fair
Campbell, 2003 Italy	No	Yes	No	Fair

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	External Validity Number screened/eligible/enrolled	External Validity Exclusion criteria
Muirhead, 1999 Canada	Number screened not reported/number eligible not reported/122 enrolled	Ineffective birth conrol method; ACEI, CCB use within 28 days prior to randomization; "brittle" diabetes; history of noncompliance with medical regimens
Andersen, 2000 Denmark	Number screened not reported/number eligible not reported/16 enrolled	History of malignant HTN, CHF, MI, or stroke within previous 3 months
Campbell, 2003 Italy	Number screened not reported/number eligible not reported/24 enrolled	Contraindication to withdrawal or treatment with ACEIs or AIIRAs; treatment with steroids, NSAIDs, immunomodulators, cytostatic agents within past 6 months; renovascular disease; obstructive uropathy; unstable angina; AMI or CVA within past 6 months; NYHA class II-IV HF; serum potassium > 6 mEq/L, despite control of metabolic acidosis; clinically significant hepatic disease (SGOT or SGPT > 3 times upper limit normal or bilirubin > 1.5 mg/dL); white blood cell count < 3000/mm3; clinical suspicion of renal vein thrombosis; known hypersensitivity to ACEIs or AIIRAs; cancer; collagen vascular disease; treatment with other investigational drugs; pregnancy, breast feeding, or ineffective contraception

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?
Muirhead, 1999 Canada	Yes	No	Yes
Andersen, 2000 Denmark	Yes	No	Yes
Campbell, 2003 Italy	Yes	No	Yes

Quality Table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Funding	Relevance?
Muirhead, 1999 Canada	Supported by a research grant from Novartis	Yes
Andersen, 2000 Denmark	Supported by a medical school grant from Merck, Sharp & Dohme	Yes
Campbell, 2003 Italy	Co-author from Novartis Farma. No funding source noted	Yes

Quality Table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

Author, Year Country	Internal Validity: Randomization adequate?	Internal Validity: Allocation concealment adequate?	Internal Validity: Groups similar at baseline?
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Method not reported	Yes	Yes except for a lower percent of female patients in the placebo group (29% vs. 35% on irbesartan and 31% on amlodipine; P=0.02) Also lower percent of non-Hispanic black patients on irbesartan (11% vs. 15% on amlodipine, 14% on placebo)
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Method not reported	Method not reported	Yes
Plum, 1998 Country not reported	Not reported	Not reported	Yes

Quality Table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

Author, Year Country	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Yes	Yes	Yes	Yes
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Yes	Yes	Yes	Yes
Plum, 1998 Country not reported	Yes	Yes, but method not described	Yes, but method not described	Yes, but method not described

Quality Table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Yes/No/No/No	No	Yes	Unable to determine
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Yes/No/No/No	No	Yes	Unable to determine
Plum, 1998 Country not reported	Yes/No/No/No	No	Yes	No

Quality Table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

Author, Year Country	Quality Rating	External Validity: Number screened/eligible/enrolled	External Validity: Exclusion criteria
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Good	Number screened not reported/number eligible not reported/1715 enrolled	Onset of type 2 DM < 20yrs of age, type 1 DM, treatment requiring ACEI, AIIRA, or CCB, CVD (including unstable angina, MI, CABG or PTCA within previous 3 months, NYHA class III or IV HF, TIA within previous 6 months, stroke within previous 3 months), abnormal serum potassium
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Good	Number screened not reported/number eligible not reported/1513 enrolled	Type 1 DM or nondiabetic renal disease (including renal artery stenosis), MI or CABG within previous month, stroke or PTCA within previous 6 months, TIA within previous year, history HF
Plum, 1998 Country not reported	Fair	Number screened not reported/number eligible not reported/9 enrolled	Increase of serum creatinine over 30% within 6 months before the trial; history of heart failure, malignancy, or any disorders requiring immunosuppressive therapy

Quality Table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Yes	No	Yes
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Yes	No	Yes
Plum, 1998 Country not reported	3-month run-in period	No	Yes

Quality Table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

Author, Year Country	Funding	Relevance?
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Supported by the Bristol-Myers Squibb Institute for Medical Research and Sanofi Synthelabo (biostatistics and data management department of sponsor was responsible for handling the data including data entry, data base review, and audit)	Yes
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Supported by Merck and company (one employee of sponsor was a non-voting member of both the steering and safety committees; the steering committee supervised the study design, conduct of the trial, and management and analysis of the data and a subcommittee of which prepared the report)	Yes
Plum, 1998 Country not reported	Supported by Novartis	Yes

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Benz et al 1997	Method not reported	Not reported	93% of valsartan and 100% of lisinopril and HCTZ groups had significant medical history and/or concomitant diagnoses; otherwise similar.	Yes
Chan et al 1997 Taiwan and Hong Kong	Method not reported	Not reported	Yes	Yes
Elliot 1999 US	Method not reported	Not reported	Yes	Yes
Fogari et al 2001 Italy	Method not reported	Not reported	Yes	Yes
Fogari et al 2002 Italy	Method not reported	Not reported	Not reported	Yes

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Benz et al 1997	Yes	Not reported	Yes	Yes/No/No/No
Chan et al 1997 Taiwan and Hong Kong	Yes	Not reported	Yes	No
Elliot 1999 US	Yes	Not reported	Yes	No
Fogari et al 2001 Italy	Yes	Not reported	Yes	Yes/No/No/No
Fogari et al 2002 Italy	Yes	Not reported	Yes	No

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Benz et al 1997	No	1/129 not analyzed	No	Fair
Chan et al 1997 Taiwan and Hong Kong	Not reported	Unable to assess- number analyzed not reported	Not reported	Poor
Elliot 1999 US	Not reported	Unable to assess- number analyzed not reported	Not reported	Poor
Fogari et al 2001 Italy	No	No	No	Fair
Fogari et al 2002 Italy	Not reported	Unable to assess- number analyzed not reported	Not reported	Poor

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Number screened/eligible/enrolled	Exclusion criteria
Benz et al 1997	197 screened/141 eligible/129 enrolled	Clinical heart failure, second or third degree heart block, angina, significant dysrhythmias, valvular heart disease, evidence of hepatic or renal impairment, insulin-dependent diabetes mellitus, pregnancy, history in past 6 months of MI, hypertensive encephalopathy, or cerebrovascular accident, any respiratory condition associated witha cough, and history of smoking within past 2 years.
Chan et al 1997 Taiwan and Hong Kong	Number screened/eligible not reported/84 enrolled	Known intolerance to trial drugs, diabetes, clinically significant laboratory abnormalities, and use of aspirin, NSAIDs, or antitussive agents.
Elliot 1999 US	Not reported	Secondary forms of hypertension, advanced hypertensive retinopathy, average sitting systolic blood pressure >200 mmHg, advanced atrioventricular conduction defects, ventricular tachyarrhythmias requiring therapy, bradycardia, prior myocardial infarction or cerebrovascular accident within past 90 days, congestive heartfailure being treated with nitrates, beta-blockers or calcium channel blockers, unstable diabetes mellitus, or presence of clinically significant renal or hepatic disease or another concurrent severe disease, conditions which could interfere with the assessment of cough: emphysema, asthma or chronic bronchitis, or upper respiratory infectino within 2 weeks of screening; use of anticoagulants or another investigational drug within 30 days of enrollment, chronic sympathomimetic amine or NSAIDs (other than low-dose aspirin) within 7 days of enrollment, and concomitant use of antidepressants or medications known to affect blood pressure or cough.
Fogari et al 2001 Italy	Number screened, eligible not reported/160 enrolled	Diabetes mellitus, obesity, smoking habits, major cardiovascular and noncardiovascular diseases, or conditions requiring any other concomitant medication.
Fogari et al 2002 Italy	Number screened, eligible not reported/110 enrolled	Diabetes mellitus, obesity, smoking habits, major cardiovascular and noncardiovascular diseases, or conditions requiring any other concomitant medication.

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Benz et al 1997	2-4 weeks placebo washout, then 2-4 weeks lisinopril run-in, then 2 more weeks placebo washout.	No	Yes	Not reported	All had hisory of ACE-inhibitor associated cough.
Chan et al 1997 Taiwan and Hong Kong	Up to 8 weeks lisinopril run-in, 4 weeks placebo washout.	No	Yes	Not reported	All had hisory of ACE-inhibitor associated cough.
Elliot 1999 US	3-5 weeks placebo run-in	No	Yes	Supported by grants and contracts from SmithKline Beecham Pharmaceuticals Inc.	Releva nt
Fogari et al 2001 Italy	4 weeks placebo run-in	Yes- all newly-diagnosed, previously untreated hypertension	Yes	Not reported	Men with newly-diagnosed hypertension, excluded if experienced erectile dysfunction
Fogari et al 2002 Italy	4 weeks placebo run-in	Yes- all newly-diagnosed, previously untreated hypertension	Yes	Not reported	Men with newly-diagnosed hypertension, excluded if experienced erectile dysfunction

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Method not reported	Not reported	More white patients in lisinopril group (98%) than losartan (81%), p<0.05; otherwise similar.	Yes
Lacourciere 1999 Canada	Method not reported	Not reported	Yes	Yes
Paster et al 1998 US	Method not reported	Not reported	Yes	Yes

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Yes	Not reported	Yes	No
Lacourciere 1999 Canada	Yes	Not reported	Yes	Yes/No/No/No (1 protocol violation, but type not specified)
Paster et al 1998 US	Yes	Not reported	Yes	Yes/No/No/No (1 protocol violation, but type not specified)

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Not reported	Yes	No	Fair
Lacourciere 1999 Canada	No	No, 88/92 (96%) analyzed	Yes- 4/92: 3 due to adverse events and 1 due to protocol violations.	Fair
Paster et al 1998 US	No	No, 97/100 (97%) analyzed	Yes, but 97/100 analyzed	Fair

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Number screened/eligible/enrolled	Exclusion criteria
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Number screened, eligible not reported/135 enrolled	Clinically significant laboratory abnormalities, concomitant medications that could alter blood pressure, diabetes mellitus, pregnant or lactating women.
Lacourciere 1999 Canada	216 screened/135 eligible/92 enrolled	Women of childbearing capacity who were not using an effective method of contraception, known or suspected secondary hypertension, clinically significant pulmonary conditions, upper respiratory infections or allergic rhinitis associated with cough, smokers or those who had quit within one year of this study, cardiovascular, metabolic, hepatic, or renal dysfunction.
Paster et al 1998 US	Number screened, eligible not reported/100 enrolled	Other concurrent diseases or medical conditions or taking a medication that could pose a risk to the patient if he or she participated in the study, preclude study completion, or confound interpretation of the study results; clinically significant cardiovascular disease other than uncomplicated essential hypertension, pulmonary disease, clinically significant laboatory abnormalities, and known sensitivity to ACE inhibitors; current smokers or smokers within the preceding year, using concurrent medications that could alter blood pressure, or pregnant or lactating.

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	6 weeks lisinopril run-in, at least 2 weeks placebo washout	No	Yes	Supported in part by a grant from Merck Research Laboratories	All had hisory of ACE-inhibitor associated cough.
Lacourciere 1999 Canada	6 weeks lisinopril run-in, 4 weeks placebo washout	No	Yes	Not reported	All had hisory of ACE-inhibitor associated cough.
Paster et al 1998 US	Up to 6 weeks lisinopril run-in, 4 weeks placebo washout.	No	Yes	Funding not specified; 6 of 7 authors, including corresponding author, from Merck Research Laboratories	All had hisory of ACE-inhibitor associated cough.

Quality Table 10. Quality assessment of adverse events trials with angiotensin II receptor antagonists

Author, year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?
Biswas et al 2002 England	Yes	NA- not prospective	Yes	Yes
Benz et al 1997	Yes	Yes	Yes	Yes
Chan et al 1997 Taiwan and Hong Kong	Yes	Not reported	Yes	Yes
Elliot 1999 US	Yes	Not reported	Yes	Yes
Fogari et al 2001 Italy	Yes	Yes	Yes	Yes
Fogari et al 2002 Italy	Yes	Not reported	Yes	Yes
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Yes	Not reported	Yes	Yes
Lacourciere 1999 Canada	Yes	Yes	Yes	Yes

Quality Table 10. Quality assessment of adverse events trials with angiotensin II receptor antagonists

Author, year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality
Biswas et al 2002 England	No- only patients whose doctor returned a form were assessed; low response rate (55%)	No	Yes for some events- covered events taking place 6 months or less after initiation of treatment.	Fair
Benz et al 1997	Yes	No	Yes for cough	Fair
Chan et al 1997 Taiwan and Hong Kong	Yes	No	Yes for cough	Fair
Elliot 1999 US	Yes	Adjusted for center, regimen, and center by regimen interaction	Yes for cough	Fair
Fogari et al 2001 Italy	Yes	No	Yes for decrease in sexual activity	Fair
Fogari et al 2002 Italy	Yes	No	Yes for decrease in sexual activity	Fair
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Yes	No	Yes for cough	Fair
Lacourciere 1999 Canada	Yes	Subgroup analyses by sex, age, and race.	Yes for cough	Fair

Quality Table 10. Quality assessment of adverse events trials with angiotensin II receptor antagonists

Author, year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?
Paster et al 1998 US	Yes	Yes	Yes	Yes

Quality Table 10. Quality assessment of adverse events trials with angiotensin II receptor antagonists

Author, year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality
Paster et al 1998 US	Yes	No	Yes for cough	Fair

Appendix A. Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2003>
Search Strategy:

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1 (Losartan or cozaar).mp. (438)
2 (Telmisartan or Micardis).mp. (38)
3 (Candesartan or Atacand).mp. (129)
4 (Eprosartan or Tevetan).mp. (39)
5 (Irbesartan or Avapro).mp. (102)
6 (Olmesartan or Benicar).mp. (3)
7 (Valsartan or Diovan).mp. (109)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (792)
9 from 8 keep 1-792 (792)

Database: MEDLINE <1989 to November 2003>
Search Strategy:

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1 (Losartan or cozaar).mp. (3879)
2 (Telmisartan or Micardis).mp. (151)
3 (Candesartan or Atacand).mp. (570)
4 (Eprosartan or Tevetan).mp. (157)
5 (Irbesartan or Avapro).mp. (440)
6 (Olmesartan or Benicar).mp. (37)
7 (Valsartan or Diovan).mp. (483)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (5120)
9 congestive heart failure.mp. or exp Heart Failure, Congestive/ (32693)
10 Hypertension/ or high blood pressure.mp. (61129)
11 diabetes mellitus.mp. or exp Diabetes Mellitus/ (100384)
12 myocardial infarct$.mp. or exp Myocardial Infarction/ (59758)
13 9 or 10 or 11 or 12 (235914)
14 8 and 13 (2068)
15 exp Randomized Controlled Trials/ or rct.mp. (29585)
16 systematic review$.mp. (4402)
17 15 or 16 (32622)
18 14 and 17 (153)
19 from 18 keep 1-153 (153)

Database: EMBASE Drugs & Pharmacology <1991 to 4th Quarter 2003>
Search Strategy:
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1 (Losartan or cozaar).mp. (5350)
2 (Telmisartan or Micardis).mp. (422)
3 (Candesartan or Atacand).mp. (1323)
4 (Eprosartan or Tevetan).mp. (414)
5 (Irbesartan or Avapro).mp. (1069)
6 (Olmesartan or Benicar).mp. (102)
7 (Valsartan or Diovan).mp. (1157)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (7297)
9 congestive heart failure.mp. or exp Congestive Heart Failure/ (10549)
10 Hypertension/ or high blood pressure.mp. (49080)
11 diabetes mellitus.mp. or exp Diabetes Mellitus/ (63354)
12 myocardial infarct$.mp. or exp Myocardial Infarction/ (34624)
13 9 or 10 or 11 or 12 (140693)
14 8 and 13 (3559)
15 exp Randomized Controlled Trials/ or randomized controlled trial$.mp. or rct.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (64610)
16 systematic review$.mp. (1579)
17 practice guideline.mp. or exp Practice Guideline/ (30590)
18 meta-analysis.mp. or exp meta analysis/ (12616)
19 multicenter study.mp. or exp multicenter study/ (22413)
20 controlled clinical trial$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (3620)
21 16 or 17 or 18 or 19 or 20 (66788)
22 14 and 21 (490)
23 limit 22 to (human and english language) (449)
24 limit 23 to (adult <18 to 64 years> or aged <65+ years>) (181)
25 from 24 keep 1-181 (181)
26 from 25 keep 1-181 (181)

Appendix B. Criteria for Rating Observational Studies of Adverse Events

For use with controlled trials (designed to assess efficacy or adverse events) and observational studies of adverse events.

1. Non-biased selection
    - Yes (RCT or observational study with inception cohort in which all patients were assessed for adverse events.
    - Not clear
    - No

2. Low overall loss to follow-up
    - Yes
    - Not clear (withdrawn not reported, or no patients reported withdrawn although other studies of studies of patients on similar drugs report high withdrawal)
    - No (overall proportion depends on topic)

3. Adverse events pre-specified or defined
    - Yes (study reports definitions used for adverse events in an explicit, reproducible fashion)
    - No

4. Ascertainment techniques adequately described
    - Yes (Study reports methods used to ascertain complications, including who ascertained, timing, and methods used)
    - No

5. Non-biased and accurate ascertainment of adverse events
    - Yes (patients and assessors blinded to intervention, and ascertainment techniques valid)
    - No

6. Statistical analysis of potential confounders
    - Yes (study examines relevant confounders/risk factors using standard acceptable statistical techniques)
    - No

7. Adequate duration of follow-up
    - Yes (study reports duration of follow-up and duration of follow-up adequate to identify expected adverse events)
    - No

8. Overall quality score (Either use a point system, or Good=meets all criteria, Poor=fatal flaw, Fair= all other)
    - Good, Fair, Poor

Appendix C. Bibliography of Included Articles

Anonymous. Evaluation of candesartan cilexetil in black patients with systemic hypertension: the ABC Trial. *Heart Dis* 2000;2(6):392-9. [Rec#: 1076]
Notes: Included: Discussion.

American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care 2003* 26(Suppl 1);S80-2. [Rec#: 40]
Notes: Included: Background.

Anderson S, Tarnow L, Rossing P, Hansen BV, Parving HH. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. *Kidney Int* 2000;57:601-6. [Rec#: 38]
Notes: Included: ACT Nephropathy.

Argenziano L, Trimarco B: Effect of eprosartan and enalapril in the treatment of elderly hypertensive patients: subgroup analysis of a 26-week, double-blind, multicentre study. Eprosartan Multinational Study Group. *Current Medical Research & Opinion* 1999;15:9-14. [Rec#: 154]
Notes: Included: Subgroup Key Question.

Benz J, Oshrain C, Henry D, Avery C, Chiang YT, Gatlin M: Valsartan, a new angiotensin II receptor antagonist: a double-blind study comparing the incidence of cough with lisinopril and hydrochlorothiazide. *Journal of Clinical Pharmacology* 1997;37:101-7. [Rec#: 190]
Notes: Included: Safety Key Question.

Biswas PN, Wilton LV, Shakir SW: The safety of valsartan: Results of a postmarketing surveillance study on 12 881 patients in England. *Journal of Human Hypertension* 2002;16:795-803. [Rec#: 202]
Notes: Included: Safety Key Question.

Breeze E, Rake EC, Donoghue MD, Fletcher AE: Comparison of quality of life and cough on eprosartan and enalapril in people with moderate hypertension. *Journal of Human Hypertension* 2001;15:857-62. [Rec#: 213]
Notes: Included: ACT HTN.

Brenner BM, Cooper ME, De Zeeuw D, et al. for the RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-9. [Rec#: 32]
Notes: Included: PCT Nephropathy.

Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. *Clin Pharmacol Ther* 1996;60(1):8-13. [Rec#: 1075]
Notes: Included: Discussion.

Campbell R, Sangalli F, Perticucci E, et al. Effects of combined ACE inhibitor and angiotensin II antagonist treatment in human chronic nephropathies. *Kidney International* 2003;63(3):1094-1103.
Notes: Included: ACT Nephropathy.

Chan P, Tomlinson B, Huang TY, Ko JT, Lin TS, Lee YS: Double-blind comparison of losartan, lisinopril, and metolazone in elderly hypertensive patients with previous angiotensin-converting enzyme inhibitor-induced cough. *Journal of Clinical Pharmacology* 1997;37:253-7. [Rec#: 238]
Notes: Included: Safety Key Question.

Cohn JN, Tognoni G, for the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75. [Rec#: 16]
Notes: Included: PCT HF.

Conlin PR, Spence JD, Williams B, et al: Angiotensin II antagonists for hypertension: are there differences in efficacy?[comment]. *American Journal of Hypertension* 2000;13:418-26. [Rec#: 268]
Notes: Included: Background.

Cowley AJ, Wiens BL, Segal R, et al: Randomised comparison of losartan vs. captopril on quality of life in elderly patients with symptomatic heart failure: the losartan heart failure ELITE quality of life substudy. *Quality of Life Research* 2000;9:377-84. [Rec#: 273]
Notes: Included: ACT HF.

Dahlöf B, Devereux R, de Faire U, et al: The Losartan Intervention For Endpoint reduction (LIFE) in Hypertension study: rationale, design, and methods. The LIFE Study Group. *American Journal of Hypertension* 1997;10:705-13. [Rec#: 279]
Notes: Included: Discussion.

Dahlöf B, Devereux RB, Kjeldsen SE, et al. for the LIFE study group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE). a randomized trial against atenolol. *Lancet* 2002;359:995-1003. [Rec#: 11]
Notes: Included: ACT CV .

Dahlöf B, Lindholm LH, Carney S, Pertti J, Ostergren J: Main results of the losartan versus amlodipine (LOA) study on drug tolerability and psychological general well-being. *Journal of Hypertension* 1997;15:1327-1335. [Rec#: 283]
Notes: Included: ACT HTN.

De Rosa ML, Cardace P, Rossi M, Baiano A, de Cristofaro A: Comparative effects of chronic ACE inhibition and AT1 receptor blocked losartan on cardiac hypertrophy and renal function in hypertensive patients. *Journal of Human Hypertension* 2002;16:133-40. [Rec#: 291]
Notes: Included: ACT HTN.

Devereux RB, Dahlöf B, Kjeldsen SE, et al. , for the LIFE Study Group . Effects of losartan or atenolol in hypertensive patients without clinically evident vascular disease. a substudy of the LIFE randomized trial. *Ann Intern Med* 2003;139:169-77. [Rec#: 14]
Notes: Included: ACT CV.

Dickstein, K, Kjekshus, J, Committee OTS, Investigators.Optimal Trial in Myocardial Infarction with the Angiotensin IIAL: Comparison of baseline data, initial course, and management: losartan versus captopril following acute myocardial infarction (The OPTIMAAL Trial). OPTIMAAL Trial Steering Committee and Investigators. Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan. *American Journal of Cardiology* 2001;87:766-771. [Rec#: 309]
Notes: Included: Discussion.

Dickstein K, Chang P, Willenheimer R, et al: Comparison of the effects of losartan and enalapril on clinical status and exercise performance in patients with moderate or severe chronic heart failure. *Journal of the American College of Cardiology* 1995;26:438-45. [Rec#: 312]
Notes: Included: ACT HF.

Dickstein K, Kjekshus J: Comparison of the effects of losartan and captopril on mortality in patients after acute myocardial infarction: The OPTIMAAL trial design. *American Journal of Cardiology* 1999;83:477-481. [Rec#: 314]
Notes: Included: Discussion.

Dickstein K, Kjekshus J, and the OPTIMAAL Steering Committee, for the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction. the OPTIMAAL randomized trial. *Lancet* 2002;360:752-60. [Rec#: 28]
Notes: Included: ACT MI.

Dunselman PH, Replacement of Angiotensin Converting Enzyme Inhibition I: Effects of the replacement of the angiotensin converting enzyme inhibitor enalapril by the angiotensin II receptor blocker telmisartan in patients with congestive heart failure. The replacement of angiotensin converting enzyme inhibition (REPLACE) investigators. *International Journal of Cardiology* 2001;77:131-8. [Rec#: 324]
Notes: Included: ACT HF.

Elliot WJ: Double-blind comparison of eprosartan and enalapril on cough and blood pressure in unselected hypertensive patients. *Journal of Human Hypertension* 1999;13:413-417. [Rec#: 331]
Notes: Included: Safety Key Question.

Flack JM, Saunders E, Gradman A, et al: Antihypertensive efficacy and safety of losartan alone and in combination with hydrochlorothiazide in adult African Americans with mild to moderate hypertension.[erratum appears in Clin Ther 2001 Nov;23(11):1922]. *Clinical Therapeutics* 2001;23:1193-208. [Rec#: 350]
Notes: Included: Subgroup Key Question.

Fogari R, Preti P, Derosa G, et al: Effect of antihypertensive treatment with valsartan or atenolol on sexual activity and plasma testosterone in hypertensive men. *European Journal of Clinical Pharmacology* 2002;58:177-80.
Rec#: 359]
Notes: Included: Safety Key Question.

Fogari R, Zoppi A, Poletti L, Marasi G, Mugellini A, Corradi L: Sexual activity in hypertensive men treated with valsartan or carvedilol: a crossover study. *American Journal of Hypertension* 2001;14:27-31. [Rec#: 364]
Notes: Included: Safety Key Question.

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