Drug Class Review on Angiotensin Converting Enzyme Inhibitors

Final Report

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Introduction

Angiotensin-converting-enzyme-inhibitors (ACEIs) block the activation of the renin-aldosterone system, an important mediator of blood pressure. In addition to their effects on blood pressure, ACEIs are also thought to have beneficial effects on ventricular remodeling following myocardial infarction and in patients with heart failure, and on preventing the progression of diabetic nephropathy. The American Heart Association and American College of Cardiology recommend ACEIs as standard therapy in patients with recent myocardial infarction,[1] in patients with systolic heart failure,[2] and in patients at high risk for cardiovascular events.[3] In addition, the American Diabetes Association recommends ACEIs as standard treatment for patients with diabetic nephropathy.[4]

As of April 2004, eleven ACEIs were marketed in North America: benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril. These drugs have Food and Drug Administration (FDA) indications for treating hypertension, heart failure, secondary prevention of myocardial infarction, and diabetic nephropathy (see Table 1). ACE inhibitors (with the exception of captopril and lisinopril) are prodrugs requiring activation through hepatic biotransformation. Most ACEIs have half-lives of 10-12 hours; the shortest-acting are captopril (<2 hours) and quinapril (2 hours), while the longest acting is ramipril (13-17 hours). ACEIs are eliminated mainly by the kidneys and to a lesser extent through the liver. Benazepril, captopril, enalapril, and lisinopril are less dependent on hepatic elimination than the other ACEIs. All ACEIs except fosinopril require dose adjustment in renal failure (creatinine clearance <30 ml/min).

The role of ACEIs in treating patients who have high blood pressure is evolving. In May 2003 the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) published an "express" version of their new recommendations.[5] JNC-7 recommends thiazide diuretics as the first-line option for patients with Stage-1 hypertension who do not have compelling indications for another agent. JNC-7 notes that most patients will eventually need 2 drugs to control hypertension. For patients with Stage-2 hypertension (SBP>160 or DBP>100), JNC-7 recommends starting therapy with 2 drugs, usually a diuretic plus an ACEI, beta-blocker, or calcium channel blocker. ACEIs are recommended as one of several acceptable first-line options for patients who have hypertension in combination with one of the following "compelling indications": heart failure, diabetes, chronic kidney disease, high cardiovascular risk, a history of myocardial infarction, or a history of stroke.

Scope and key questions

The purpose of this review is to compare the efficacy and adverse effects of different ACE Inhibitors. The Oregon Evidence-based Practice Center 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:

Key Question 1. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do angiotensin converting enzyme inhibitors differ in efficacy?

Key Question 2. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do angiotensin converting enzyme inhibitors differ in safety or adverse events?

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one angiotensin converting enzyme inhibitor is more effective or associated with fewer adverse events?

Table 1. FDA indications for ACEIs

Drug	High Blood Pressure	Heart Failure or Heart Failure after MI	Recent MI	Diabetic nephropathy	Reduction in risk of myocardial infarction, stroke, and death from cardiovascular causes.	Half-Life	Elimination
Benazepril (Lotensin)	Yes					10-11 hours**	Predominantly renal, 11%-12% biliary
Captopril (Capoten)	Yes	Yes*	Yes	Yes		<2 hours	>95% renal
Cilazapril (Inhibace, Canada)	Yes	Yes				7-11 hours	Renal
Enalapril (Vasotec)	Yes	Yes*				11 hours**	60% renal, 33% fecal
Fosinopril (Monopril)	Yes	Yes				12 hours**	50% renal, 50% fecal
Lisinopril (Prinivil, Zestril)	Yes	Yes	Yes			12 hours	Predominantly renal
Moexipril (Univasc)	Yes					2-9 hours**	13% renal, 53% fecal
Perindopril (Aceon)	Yes					3-10 hours**	75% renal, 25% fecal
Quinapril (Accupril)	Yes	Yes				2 hours**	60% renal, 37% fecal
Ramipril (Altace)	Yes	Yes (HF)			Yes	13-17 hours**	60% renal, 40% fecal
Trandolapril (Mavik)	Yes	Yes (HF & LV Dysfx)				10 hours**	33% renal, 56% fecal

*Also indicated for asymptomatic LV dysfunction. HF=heart failure, LV=left ventricle, Dysfx=dysfunction

**Of active metabolite

Methods

To identify articles relevant to each key question, we searched (in this order): the Evidence-Based Medicine Library (2003, Issue 4) (from the Cochrane Collaboration), MEDLINE (1966-February Week 3 2004), EMBASE (1980-1st Quarter 2004), Premedline (through March 1, 2004), and reference lists of review articles. In electronic searches we used broad searches, combining terms for included ACEIs with terms for relevant clinical outcomes and patient populations (see Appendix A for complete search strategy). In addition, pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote 6.0).

Study selection

All English-language titles and abstracts and suggested additional citations were reviewed for inclusion, using the criteria outlined in the key questions. The citations were divided between two reviewers and assessed for inclusion. One reviewer then assessed for inclusion full articles, with consultation from a second reviewer where necessary.

The key questions specified the following patient *populations*: hypertension, high cardiovascular risk, recent myocardial infarction, heart failure, diabetic nephropathy, and nondiabetic nephropathy. Study populations overlap these categories. For example, many patients with hypertension also have other cardiovascular risk factors or heart failure. Many patients who have heart failure are also "recent myocardial infarction" patients; also, ACEIs are used to prevent *symptomatic* heart failure in recent myocardial infarction patients who have *asymptomatic* left ventricular systolic dysfunction.

To avoid redundancy, we defined the following categories, which we used to classify studies:

Hypertension without compelling indications. This refers to patients who have hypertension but do not have

- a history of coronary heart disease (CHD)
- other cardiovascular diseases (CVD), such as cerebrovascular (carotid) disease, peripheral vascular disease, or a history of stroke
- diabetes
- other risk factors for CAD/CVD, such as smoking or hyperlipidemia
- renal insufficiency

Hypertension with compelling indications. This refers to patients with hypertension who also have one of the conditions listed above.

High cardiovascular risk. This group includes patients who have a history of CHD/CVD, diabetes, or a combination of other risk factors for CHD/CVD, such as smoking and hyperlipidemia. These patients may or may not have hypertension as well.

Recent myocardial infarction. This group includes patients who have had a recent myocardial infarction and who have normal left ventricular function *or* asymptomatic left ventricular dysfunction.

Heart failure. This group includes patients who have symptomatic heart failure due to left ventricular systolic dysfunction, with or without hypertension.

Diabetic nephropathy. This group includes patients with Type 1 or Type 2 diabetes who have laboratory evidence of nephropathy, such as albuminuria or decreased creatinine clearance.

Nondiabetic nephropathy. This group includes patients without diabetes who have laboratory evidence of nephropathy, such as decreased creatinine clearance.

Included *interventions* were treatment with benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, perindopril, or trandolapril. Included *outcomes* varied according to the clinical condition and are listed in Table 2 below:

Table 2. Outcomes of treatment with ACEIs

Hypertension*	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure) 3. 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) 4. Quality-of-life
High cardiovascular risk	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure)
Recent-myocardial infarction	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Heart failure	1. All-cause or cardiovascular mortality 2. Symptomatic improvement (heart failure class, functional status, visual analogue scores) 3. Hospitalizations for heart failure
Diabetic nephropathy	1. 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)
Nondiabetic nephropathy	1. 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)

*Trials that focused on blood pressure reduction but not on any health outcomes were excluded from the efficacy review.

In addition to these outcomes, we assessed for important adverse events associated with ACEIs including hypotension, cough, angioedema, and hyperkalemia. In some studies, only 'serious' or 'clinically significant' adverse events are reported. Some studies do not define these terms, and in others, the definitions varied.

We obtained full-text articles if the title and abstract review met the following criteria:

1. Systematic reviews of the clinical efficacy or adverse event rates of ACEIs for included clinical conditions that reported an included outcome, or
2. Randomized controlled trials that compared one of the included ACEIs to another included ACEI, or
3. Large (> 100 patients) placebo-controlled trials for included clinical conditions that reported an included outcome, or
4. Randomized controlled trials and large, good-quality observational studies that evaluated adverse event rates for one or more of the included ACEIs.

Full-text articles were included in the systematic review if they met the above criteria and reported clinical efficacy or adverse event rates from specific ACEIs. While we preferred studies of longer duration, we had no lower limit on the length of follow-up, but excluded "single-dose studies" examining the effects of a single dose of medication rather than a course of treatment or studies that evaluated inpatients before hospital discharge. We excluded trials of ACEIs in combination with another cardiovascular drug when the effect of the ACEI could not be isolated.

Data abstraction

The following data was abstracted from included trials: study design, setting, population characteristics (including sex, age, race, 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 the trial did not report high overall loss to follow-up.

Validity assessment

We assessed quality of trials based on the predefined criteria listed in Appendix B, which were submitted to the Health Resources Commission in December 2001 and updated in February 2003. We rated the internal validity of each trial based on methods used for randomization; allocation concealment and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up (less than 15%); and the use of intention-to-treat analysis. External validity of trials was assessed based on: adequate description of the study population; similarity of patients to other populations to whom the intervention would be applied; control group receiving comparable treatment; funding source; and role of the funder.

Overall quality was assigned based on criteria developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[6, 7] Trials with a fatal flaw in one or more categories were rated poor-quality. Trials that met all criteria were rated good-quality. The remainder were rated fair-quality. As the "fair-quality" category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are *unlikely* to be valid, while others are *probably* or *likely* to be valid. The details of the quality assessment of individual studies are provided in evidence tables. A "poor-quality" trial is not valid. The results are at least as likely to reflect flaws in the study design as they are true differences between the compared drugs. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events.

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

Data synthesis

We constructed evidence tables showing study characteristics, quality ratings, and results for all included studies. Poor-quality studies would usually be excluded from evidence tables, but we included them to ensure that the reader is familiar with their limitations.

To assess the overall strength of evidence for a body of literature about a particular key question, we examined the consistency of study designs, patient populations, interventions, and results. Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered "good-quality.") For a body of fair-quality studies, however, consistent results may indicate that similar biases are operating in all the studies. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the overall body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm.

Results

Overview

Searches identified 6,097 citations from electronic sources, reference lists, and pharmaceutical company submissions (Figure 1). The numbers of articles that met the inclusion criteria for each question are described below.

Most of the randomized trials had fair or good internal validity, but their applicability to community practice was difficult to determine. The treatment and control groups generally received other standard therapies for the condition evaluated, but current therapies varied depending on the date of publication and local practices. Most studies did not report numbers of patients screened or eligible for treatment. Most trials excluded patients with significant co-morbid medical conditions or 'compelling' indications or contraindications for ACEI therapy, and one trial reported that excluded patients had significantly worse outcomes than enrolled patients.[8] Some studies did not state the source of funding, but almost all that reported funding sources were funded at least in part by the pharmaceutical industry.

Key Question 1: For adult patients with various indications, do angiotensin converting enzyme inhibitors differ in efficacy?

1a.1. Hypertension without compelling indications

Mortality and cardiovascular events. A recent, comprehensive meta-analysis identified 42 controlled trials of anti-hypertension drugs reporting major cardiovascular disease end points and all-cause mortality.[9] Nine trials, listed in Table 3, involved an ACEI.[10 11 12 13 14 15 16 17, 18 19, 20 21, 22] Most used a composite endpoints (e.g., mortality plus CV events). The first 4 studies in Table 3 compared an ACEI (captopril, enalapril, or lisinopril) with diuretics or beta-blockers in patients with hypertension. ALLHAT, the largest and most recent trial, provides the most definitive results. None of these trials was designed to compare one ACEI to another. In the STOP-2 trial[11] patients were assigned to several different drugs, including 2 different ACEIs, but the results of the 2 ACEIs were combined in the data analysis. As a group, these studies do not

provide useful information to compare the effectiveness of different ACEIs in patients who have high blood pressure and no compelling indications.

Quality of Life. Two head-to-head trials reported a comprehensive, validated set of quality of life outcomes, including scales measuring psychological distress, psychological well-being, general perceived health, well-being at work, and sexual symptom distress.[23,24] In one good-quality, large (n=379), 24-week head-to-head trial, blood pressure control was equivalent for captopril (25 to 50 mg twice a day) vs. enalapril (5 to 20 mg twice a day) in otherwise healthy men with essential hypertension.[23] However, as measured at the end of the followup period, patients assigned to captopril had better quality-of-life than patients assigned to enalapril. A strength of this trial is that the investigators measured several aspects of quality-of-life. Because of the detailed measurement of quality-of-life, the investigators were able to determine that, among patients who had good quality-of-life prior to starting treatment with an ACEI, those taking captopril remained stable, while those taking enalapril worsened ($p<0.001$). The major weakness of the study was that results were reported as averages for the compared groups rather than as percentages that improved, remained stable, or worsened. Because of this, it is impossible to calculate a NNT from the published results, even though it is clear that the average differences between the captopril and enalapril groups was clinically significant. The rates of adverse events and withdrawals were similar for captopril and enalapril, so adverse events did not explain the differences in quality of life.

An earlier, large (n=360), good-quality, 8-week head-to-head trial found no difference in efficacy for reducing blood pressure quality of life among hypertensive men randomized to captopril, enalapril, or beta-blockers.[24] There were also no differences in quality of life between captopril, enalapril, and atenolol, all of which were better than propranolol for preserving quality of life. Because of the short followup period, these results should not be viewed as contradicting the results of the other head-to-head trial.

1a. 2. Hypertension with compelling indications

Mortality and cardiovascular events. The second section of Table 3 lists 5 studies of patients who had hypertension as well as diabetes or a history of stroke. In two of the trials (ABCD and FACET), an ACEI (enalapril or fosinopril) was better than a calcium channel blocker to reduce the incidence of MI or the combined endpoint of MI, stroke or hospitalization for angina in patients who had diabetes and hypertension. In the next trial, a substudy of the UKPDS, captopril was equivalent to a beta blocker in patients with diabetes and hypertension.

PROGRESS compared perindopril to a placebo in hypertensive and non-hypertensive patients who had a history of stroke. Patients who did not have a definite indication for treatment with an ACEI (such as heart failure) were randomized to perindopril or placebo; in those who had an indication for a diuretic, perindopril plus a diuretic was compared with placebo.[25] Single-drug therapy with perindopril produced no discernable reduction in the risk of stroke in patients with hypertension versus placebo (risk difference 5%, confidence interval –19% to 23%).

Patients with renal insufficiency or renal disease. A recent meta-analysis of 11 randomized controlled trials reported that ACEIs reduce the risk of end-stage renal disease in patients without diabetes who have renal disease (0.69 (CI, 0.51 to 0.94).[26] In a placebo-

controlled trial, ramipril reduced the incidence of end-stage renal disease and doubling of serum creatinine in patients who had proteinuria from nondiabetic kidney diseases.[27, 28] The AASK trial (see Table 3) compared an ACEI, a beta blocker, and a calcium channel blocker in African American patients with hypertensive kidney damage. The primary outcome measure was reduction in GFR by 50% or more (or > or =25 mL/min per 1.73 m2) from baseline, end stage renal disease (ESRD), or death. Compared with the metoprolol and amlodipine groups, the ramipril group manifested risk reductions in this clinical composite outcome measure of 22% (95% CI, 1%-38%; P =.04) and 38% (95% CI, 14%-56%; P =.004), respectively.[19]

Table 3. ACEI hypertension trials with active controls or placebo controls

Trial	Patients. Followup. Mean baseline SBP/DBP.	ACE inhibitor(s)	Other drugs or groups	Comment
Hypertension without compelling indications.				
CAPPP Captopril Prevention Project	Hypertension (measured diastolic blood pressure of 100 mm Hg on two occasions) 161/99	Captopril (5492 patients)	diuretics, beta-blockers	No difference in composite of myocardial infarction, stroke, and cardiovascular deaths. (RR 1.05; 95% CI 0.90, 1.22)
STOP-2	Hypertension, large subgroups 11% had diabetes. 5 years of followup. 194/98	enalapril 10 mg lisinopril 10 mg (total of 2205 patients)	Diuretics, beta-blockers	No differences in fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease. (RR 0.99; 95% CI 0.84, 1.16)
ALLHAT	Hypertension. 4 to 8 years of followup.	Lisinopril, 10 to 40 mg/d (9054 patients)	Chlorthalidone or amlodipine	Chlorthalidone was better than amlodipine or lisinopril. chlorthalidone vs lisinopril: Combined CVD (RR 1.10; 95% CI 1.05, 1.16) Stroke (RR 1.15; 95% CI 1.02, 1.30) HF (RR 1.19; 95% CI 1.07, 1.31)
Second Australian National Blood Pressure Study	Hypertension.	Enalapril or other ACEI	HCTZ or other diuretic	ACEI were better than diuretics for CV events or all-cause mortality. (Hazard Ratio 0.89; 95% CI 0.79, 1.00)
Hypertension with compelling indications.				
ABCD Appropriate Blood Pressure Control in Diabetes	Hypertension plus Type 2 diabetes. Five years of followup.155/98	Enalapril (233 patients)	Nisoldipine	Higher incidence of MI in the nisoldipine group. (RR 9.5; 95% CI 2.3, 21.4)
FACET Fosinopril versus Amlodipine Cardiovascular Events Trial	Hypertension plus Type 2 diabetes. 2.5 years of followup.	Fosinopril (189 patients)	Amlodipine	Fosinopril had a significantly lower risk of the combined outcome of MI, stroke, or hospitalized angina (14/189 vs. 27/191) (Hazard Ratio 0.49; 95% CI 0.26, 0.95)
UKPDS	Hypertension plus Type 2 diabetes 8.4 years of followup.160/94	Captopril (400 patients)	Atenolol	No difference in macrovascular or microvascular outcomes. (RR for any diabetes related endpoint 1.10; 95% CI 0.86, 1.41)

Table 3. ACEI hypertension trials with active controls or placebo controls (continued)

Trial	Patients. Followup. Mean baseline SBP/DBP.	ACE inhibitor(s)	Other drugs or groups	Comment
AASK African American study of kidney disease and hypertension	African-American with hypertension and renal insufficiency. 3 years of followup	Ramipril (436 patients)	Metoprolol succinate or amlodipine besylate	Ramipril was better than metoprolol or amlodipine for the clinical composite outcome of reduction in GFR by 50% or more, ESRD, or death. (RR 0.78; 95% CI 0.62, 0.99 vs metoprolol; RR 0.62; 95% CI 0.44, 0.86 vs amlodipine)
PROGRESS perindopril protection against recurrent stroke study	Hypertensive and non-hypertensive patients with a history of stroke or transient ischemic attack	Perindopril alone or with a diuretic (3051 patients)	Placebo	Combination therapy reduced the risk of recurrent stroke in hypertensive patients with a history of stroke. (RR 0.0.57; 95% CI 0.46, 0.70) Perindopril alone had no effect in any subgroup. (RR 0.95; 95% CI –0.81, 0.77)

1b. High cardiovascular risk

Seven completed trials of ACEIs have enrolled patients who have coronary artery disease or who have risk factors for cardiovascular disease but not hypertension.[29] One of these was PROGRESS (Table 3),[21] which enrolled some normotensive patients who had a previous stroke. In normotensive patients who received perindopril alone, there was no reduction in the risk of recurrent stroke.

The other six trials, with the numbers-needed-to-treat to prevent major cardiovascular events, are described in Table 4 and in more detail in Evidence Table 1 (study characteristics) and Evidence Table 2 (quality assessment). For the most part, HOPE[30] should be viewed as a secondary prevention trial similar to those concerning recent myocardial infarction. About 80% of HOPE subjects had known cardiovascular disease, most commonly, a history of myocardial infarction. Nearly half had hypertension, and 38% had diabetes.

In HOPE, ramipril reduced major cardiovascular events and all-cause mortality overall in patients with diabetes, without diabetes, in those with hypertension and without hypertension, but not in patients who had no history of cardiovascular disease.

DIABHYCAR[31] was a study of patients with diabetic nephropathy. It is discussed here because its primary outcome measures were mortality and cardiovascular disease. Patients (N= 4,912) with type 2 diabetes and microalbuminuria or proteinuria were randomized to low dose (1.25 mg) ramipril or placebo. Fifty-six percent of the patients had hypertension. After 3 to 6 years of followup, ramipril had no effect on cardiovascular and renal outcomes. The relative risk of the primary outcome, a composite of cardiovascular death, non-fatal MI, stroke, heart failure leading to hospital admission, and end stage renal failure was 0.97 (95% CI 0.85 to 1.11). Results of EUROPA, a large European trial (n=12,218) of long-term treatment with perindopril 8 mg daily vs. placebo in patients with stable coronary artery disease, were recently published.[32, 33] Compared with the HOPE sample, patients in EUROPA were lower risk: fewer had diabetes (12% vs 38%) or hypertension (27% vs 47%). After 4 years of followup, there was a reduction in the combined endpoint of cardiovascular mortality, MI, or cardiac arrest in the perindopril group (RR=0.79, 95% CI 0.72-0.86; NNT=50), but all-cause mortality was not significantly reduced (RR 0.89; 95% CI 0.77-1.02).

Some methodological issues with EUROPA should be noted. Originally, this study was designed to last 3 years, and the primary endpoint was a composite of total mortality, MI, unstable angina, or cardiac arrest. Near the end of 3 years of followup, a decision was made to change the primary endpoint and to extend the trial by one more year. The relative risk for the original endpoint (included as a secondary endpoint) was 0.86 (95% CI 0.79-0.94) with a number needed to treat of 43 after 4 years.

The EUROPA Trial had a run-in period during which all patients were given perindopril for 4 weeks; 1437 (10.5%) patients were withdrawn after the run-in. In addition to several hundred patients who did not tolerate the drug, 75 patients had a major clinical event during the run-in. If these 75 patients were included in the primary composite endpoint in the perindopril group, the NNT to prevent one cardiovascular event in 4 years would be 125.

The sponsor of EUROPA, a pharmaceutical manufacturer, had a role in the study design, interpretation of the data, writing of the report, and the decision to submit the paper for publication. The role of the funder is not described in the HOPE Trial; it was funded by both the pharmaceutical industry and other sources (e.g., the Medical Research Council of Canada).
In the other three studies, all subjects had known coronary disease. QUIET,[34] an angiographic study that followed patients for only 2 years, had low power to detect a difference in cardiovascular events (n=1,750). In the SCAT[35] and PART2[36] trials, similar proportions of patients in the placebo group had major cardiovascular events. In SCAT (enalapril) there was a statistically significant reduction in these events (RR 0.47; 95% CI 0.24-0.90; NNT 16).

Table 4. Placebo-controlled trials of ACEI in patients at high cardiovascular risk

Trial, ACEI (total number of subjects) (QUALITY)	**Patients Followup**	**% men**	**Age, SBP DBP**	**NNT*, RR (CI) Comments**
HOPE Heart Outcomes Prevention Evaluation. Study Ramipril 10 mg (9,297) (FAIR)	History of CVD (80%) or diabetes (38%) plus one other risk factor (HTN—47%, High cholesterol—66%, smoking—14%). Patients with nephropathy or heart failure were excluded. Followup 5 years.	73%	66, 139 79	**NNT 26.7** **RR 0.79 (0.72-0.86)** Also reduced all-cause mortality (**NNT 56**).
EUROPA EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Perindopril 8 mg (12,218) (FAIR)	65% previous MI, 55% previous revascularization, 12% diabetes, 27% hypertension, 63% hypercholesterolemia. Mean 4.2 years followup Followup was originally to be 3 years. At the end of 3 years, the definition of primary endpoint was changed and study was extended by one year.	85%	60, 128 78 (after run-in)	**NNT=50** **RR 0.80 (0.71-0.91)** All-cause mortality RR=0.89 (0.77-1.02)

Table 4. Placebo-controlled trials of ACEI in patients at high cardiovascular risk (continued)

Trial, ACEI (total number of subjects) (QUALITY)	Patients Followup	% men	Age, SBP DBP	NNT*, RR (CI) Comments
DIABHYCAR (Non-insulin-dependent diabetes, hypertension, microalbuninuria or proteinuria, cardiovascular events, and ramipril) Study [31] Low dose ramipril (1.25 mg/day) (4,912) (FAIR)	Type 2 diabetes and microalbuminuria or proteinuria (56% had hypertension). 3-6 years followup	70%	65, 145 82	Ramipril had no effect on cardiovascular and renal outcomes (cardiovascular death, non-fatal MI, stroke, heart failure leading to hospital admission, and end stage renal failure).
PART2 Prevention of Atherosclerosis with Ramipril 5 to 10 mg (617) (FAIR)	History of CHD or CVD. Followup 4 years.	82%	61, 133 79	NNT 44.8 RR 0.83 (0.54-1.28). Trend toward reduced all-cause mortality (0.64, 0.35-1.18)
QUIET QUinapril Ischemic Event Trial 20 mg (1,750) (FAIR)	History of PTCA, normal lipid levels Followup 2 years	82%	58, 123 74	NNT 139 RR 0.88 (0.61-1.29). Too small to assess all-cause mortality.
SCAT Simvastatin/Enalapril Coronary Atherosclerosis Trial (229) (FAIR)	CHD, normal lipid levels Followup 4 years	89%	61, 130 78	**NNT 16 RR 0.47 (0.24-0.90)** Too small to assess all-cause mortality.

*For all cardiovascular events combined. **BOLD** means statistically significant.
CHD=coronary heart disease. CVD=other vascular disease. RR=relative risk reduction. CI=95% confidence interval
PTCA=percutaneous transluminal coronary angioplasty.

1c. Recent myocardial infarction

In patients who have had an MI, ACEIs are given to prevent the development or progression of heart failure and to reduce mortality.

Head-to-head trials. All-cause mortality and other outcomes were evaluated in two fair-quality head-to-head trials (Evidence Table 3).[a] The two included trials enrolled 225[37] and 212[38] patients 24 to 72 hours following onset of symptoms of myocardial infarction. Heart failure was not a requirement for entry. Both studies allowed other typical medications for myocardial infarction, and used roughly therapeutically equivalent doses of ACEI in each arm. One trial compared captopril 25 mg three times per day versus enalapril 5 mg three times per day for 12 months[37] and the other compared captopril 100 mg per day versus perindopril 8 mg per day for 6 months.[38] Both studies were rated fair-quality because of statistically significant ($p<=0.05$), potentially relevant baseline differences in intervention groups (more patients on

[a] A head-to-head trial of lisinopril vs. zofenopril was excluded because zofenopril has not been approved for use in the United States.[32] This was a good-quality trial that found no differences for mortality, severe heart failure, or other cardiovascular outcomes after 6 weeks.

beta-blockers in the captopril group in one trial[37] and lower Killip class in the captopril group in the other[38]). In addition, one trial had poorly described blinding methods[37] and the other was an open-label trial[38] (see Evidence Table 4 for quality assessments). One trial[37] reported pharmaceutical manufacturer sponsorship, and the other[38] did not report its funding sources.

Results are summarized in Evidence Table 5. In the first study (Foy), mortality was 12% (9/75) on captopril vs. 1.3% (1/75) on enalapril after 90 days (p=0.038), and 13% (10/75) vs. 3% (2/75) (p=0.022) after 12 months.[37] The primary endpoint was LV ejection fraction, which by 6 months had improved to a similar degree for enalapril and captopril.

In the other study (Lau), both mortality and tolerability were endpoints. Mortality was 13% (13/102) on captopril vs. 6% (7/110) on perindopril after 6 months (p=0.12), with no differences in the revascularization rate (21% vs. 20%).[38] Neither head-to-head trial reported rates of symptomatic heart failure as an endpoint.

Applicability to clinical practice was difficult to assess. In the trial that reported numbers screened and eligible, approximately one-half of eligible patients were enrolled.[37] Both trials enrolled patients in the acute phase of myocardial infarction, and may not be applicable to patients presenting later after myocardial infarction. Publication bias is a concern because there were no head-to-head trials with completely negative results.

Placebo-controlled trials. Three fair-quality systematic reviews summarized 18 trials to assess the effects of ACEIs on mortality following myocardial infarction.[39, 40,41] None assessed the internal validity of the included trials. The trials included in these reviews are listed in Evidence Table 6. One systematic review evaluated 15 randomized trials[37, 42-55] (n=15,104) on the effects of ACEIs given for >6 weeks shortly after acute myocardial infarction on overall mortality, cardiovascular mortality, and sudden cardiac death.[39] Several of the trials were small (fewer than 100 subjects), and one used intravenous captopril.[46] Another review evaluated four large (n>1000), short-term (4-6 weeks) placebo-controlled trials (CONSENSUS-II,[45] GISSI-3,[56] ISIS-4,[57] CCS-1[58]) of early ACEI treatment following acute myocardial infarction (n=98,496).[40] One trial (CONSENSUS II)[45] reported short- and long-term outcomes and was included in both systematic reviews. Another was a head-to-head trial, PROGRESS, which we discussed above. The third review, by the same group of researchers, evaluated data from five long-term trials in patients with left ventricular dysfunction or heart failure (SAVE, AIRE, TRACE, SOLVD treatment, SOLVD prevention).[41] No systematic review was designed to assess the comparative efficacy of different ACEIs.

Evidence Table 5 (results), Evidence Table 7(characteristics), and Evidence Table 8 (quality ratings) describe the trials that had 100 or more subjects and met our other inclusion criteria. In addition to the trials examined in the 2 previous reviews, we identified 2 other trials of ACEIs in recent myocardial infarction: FAMIS[59, 60] and the Shanghai Second Prevention of AMI trial[61, 62]). Both were rated fair-quality. One other placebo-controlled trial evaluating zofenopril, an ACEI not currently available in the U.S., was not included.[44]

Captopril was evaluated in 6 placebo-controlled trials, and enalapril, ramipril, trandolapril, lisinopril, and fosinopril in one trial each. Odds ratios for overall mortality compared to placebo overlapped for each evaluated ACEI. No clear pattern of one ACEI being superior to any other for mortality outcomes following myocardial infarction could be seen from large placebo-controlled trials. The numbers-needed-to-treat across studies are not comparable because the duration of followup varied and because the study populations differed in the severity of myocardial infarction; the presence or absence of left ventricular dysfunction, the

dose and timing of therapy; and the use of other medications. The proportion of patients receiving thrombolytics, for example, varied between studies: 44% in TRACE (trandolapril),[42] 58% in AIRE (ramipril), [43] and about 70% in ISIS-4 (captopril),[57] GISSI-3 (lisinopril)[56] and FAMIS (fosinopril).[59, 60] The results for each ACEI are summarized below and in Table 5.

Captopril has been demonstrated to reduce all-cause mortality and heart failure when given to recent MI patients who have asymptomatic LV dysfunction. In the SAVE trial, which was good-quality, mortality from all causes was significantly reduced in the captopril group (228 deaths/1115 patients, or 20 percent) as compared with the placebo group (275 deaths/1116 patients, or 25 percent, P = 0.019) after an average of 42 months. The number-needed-to-treat to prevent one death was approximately 20 patients.[55]

In the fair-quality Chinese Cardiac Study (CCS-1), which enrolled a broader spectrum of recent MI patients (with or without LV dysfunction), the combined end point (death + heart failure) was 1680/7468 (21.5%) in the captopril 12.5 mg tid group and 1733/7494 (23.1%) in the placebo group (P = 0.02). The effect on preventing heart failure alone was statistically significant, but the effect on mortality did not reach statistical significance (9.1% vs. 9.7%), except in the subgroup with anterior wall MI (8.6% vs 10.2%, NNT=63, P = 0.02). [58]

Captopril did not significantly reduce mortality in the ECCE trial,[47] but the trend favored captopril. In the Shanghai trial[61, 62], captopril reduced in-hospital (7% (33/478) vs. 18% (62/344); p<0.05) and 20-month mortality. In the CATS trial,[50] there was no significant difference in mortality rates after 3 months, but the number of deaths (9/149 in the captopril arm and 6/149 in the placebo arm) was small.

In the short-term ISIS-4 trial (good quality), captopril reduced mortality within 5 weeks of the onset of MI (2088/29028 (7.19%) captopril-allocated deaths vs 2231/29022 (7.69%) placebo; p = 0.02), which corresponds to an NNT of approximately 200 within one month.[57] The NNT was lower (about 100) in high-risk patients (i.e., a history of previous MI or with heart failure). In this trial ACEI treatment was given for 4 weeks and then stopped. The mortality advantage disappeared after additional followup.

Enalapril. As noted above, enalapril had an unexpected mortality advantage over captopril in a small, fair-quality head-to-head trial (PRACTICAL).[37] In placebo-controlled trials, however, enalapril has not been shown to reduce all-cause mortality. The largest trial, CONSENSUS-2, failed to show an advantage for enalapril in reducing all-cause mortality; in fact, the trend favored placebo (odds ratio 1.10, CI 0.93-1.31).[45] On the other hand, enalapril showed a significant advantage for reducing heart failure requiring a change in therapy (810/3044 (27%) vs. 908/3046 (30%); p<0.006) and a trend towards reducing heart failure requiring hospitalization (4% vs. 6%). In two smaller placebo-controlled trials listed in Evidence Table 7, the trend in mortality was also against enalapril.

Fosinopril. The FAMIS study enrolled 285 patients with acute MI and LV dysfunction.[59, 60] At 3 months, there was a trend towards higher mortality in the fosinopril arm (8.4% (11/131) vs. 5.2% (7/134). On the other hand, there was also a trend towards reduced heart failure in this group (20% vs. 24%). After 3 months, active intervention with fosinopril was discontinued and patients were followed up for 2 years on conventional therapy. After 2 years, fosinopril was associated with a significant reduction in the combined prevalence of death or moderate-to-severe heart failure (18% vs. 27%; p=0.04) but no significant reduction in all-cause mortality was seen (14.5% fosinopril vs. 14.1% placebo).

Lisinopril. In the short-term GISSI-3 trial, lisinopril reduced mortality at 6 weeks in a very broad spectrum of acute MI patients (6.4% vs. 7.2%, p not reported).[56] The effect persisted

for 6 months even though, according to the protocol, lisinopril was stopped after 6 weeks.[63] By 6 months, among patients randomized to lisinopril, 18.1% died or developed severe ventricular dysfunction versus 19.3% of those randomized to no lisinopril (NNT= 83, p = 0.03).[63]

Ramipril. In a good-quality trial (AIRE), ramipril [43] was associated with highly significant reductions in mortality (17% vs. 23%; p=0.002) and in the development of refractory heart failure (10% vs. 14%). AIRE enrolled 2,006 patients with clinical heart failure after MI. The mortality reduction persisted for several years.[64]

Trandalopril. TRACE, a good-quality trial, enrolled 1,749 patients who had left ventricular systolic dysfunction (ejection fraction less/equal 35 percent) immediately after suffering an MI.[42] Trandolapril reduced all-cause mortality (35% vs. 42%; p=0.001) as well as severe heart failure (14% vs. 20%, p=0.003). A smaller proportion of patients in TRACE received thrombolytics (44%) than in other placebo-controlled trials, making it difficult to compare its results to trials of other ACEIs.

Table 5. Placebo-controlled trials of ACEIs in patients with recent

Trial (total number of subjects) (QUALITY)	Duration of intervention	All-cause mortality (ACEI vs. placebo)	Symptomatic heart failure (ACEI vs. placebo)	Other outcomes (ACEI vs. placebo)
Captopril				
ISIS-4 Fourth International Study of Infarct Survival (58050) (GOOD)	4 weeks	NNT ~200 (7.19% vs. 7.69%, p=0.02)	No significant differences (17.0% vs. 17.3%)	No significant differences for re-vascularization, reinfarction, angina or stroke
CATS Captopril and Thrombolysis Study (298) (FAIR)	3 months	Trend towards higher mortality in captopril arm (6% vs. 4%, NS)	NNT ~11 (19% vs. 28%, p=0.05)	No significant differences for re-vascularization or reinfarction
ECCE Effects of Captopril on Cardiopulmonary Exercise Parameters Study (208) (FAIR)	4 weeks	NNT ~100 (2% vs. 3%, NS)	NNT ~9 for combined endpoint of death or symptomatic heart failure (6.7% vs. 17.3%, p=0.03)	Re-vascularization, reinfarction, angina not reported
CCS-1 Chinese Cardiac Study (6749) (FAIR)	4 weeks	NNT ~167 (9.1% vs. 9.7%, NS)	NNT ~59 (17.0% vs. 18.7%, p=0.01)	No significant differences for reinfarction, cardiac arrest, stroke
SAVE Survival and Ventricular Enlargement Study (2231) (GOOD)	Mean 42 months	NNT ~20 (20 vs. 25%, p=0.02)	NNT ~20 for heart failure requiring open-label ACEI (11% vs. 16%, p<0.001) and NNT ~33 (14% vs. 17%, p=0.019) for heart failure requiring hospitalization	NNT ~12 for mortality or major nonfatal event (heart failure requiring ACEI or hospitalization, or reinfarction) (32% vs. 40%, p<0.001)
Shanghai Second Prevention of Acute Myocardial Infarction	21-22 months	NNT ~11 for in-hospital mortality (7% vs. 18%, p<0.05)	NNT ~19 (5.5% vs. 10.9%, p not reported)	No significant differences for reinfarction or arrhythmia

Table 5. Placebo-controlled trials of ACEIs in patients with recent (continued)

(FAIR)				
Enalapril				

CONSENSUS II Cooperative New Scandinavian Enalapril Survival Study II (6090) (GOOD)	6 months	Trend towards higher mortality in enalapril arm (10.2% vs. 9.4%, NS)	NNT ~33 for heart failure requiring change in therapy (27% vs. 30%, p<0.006) and NNT ~50 for heart failure requiring hospitalization (4% vs. 6%, NS)	No significant differences for reinfarction
Fosinopril				
FAMIS Fosinopril in Acute Myocardial Infarction Study (285) (FAIR)	3 months	Trend towards higher mortality in fosinopril arm (8.4% vs. 5.2%, NS)	NNT ~25 (20% vs. 24%, NS)	NNT ~20 for ventricular arrhythmias (0.8% vs. 6.0%, p=0.02), no significant differences for reinfarction or re-vascularization
Lisinopril				
GISSI-3 Gruppo Italiano per lo Studio della Soprawivenza nell'Infarto Miocardico (19394) (GOOD)	6 weeks	NNT ~125 (6.4% vs. 7.2%, p not reported)	No significant differences (3.9% vs. 3.7%)	NNT ~71 for combined endpoint of mortality, clinical heart failure, ejection fraction <35%, or akinesis/dyskinesis score >45% (15.6% vs. 17.0%, p=0.009), no significant differences for reinfarction, angina, re-vascularization, or stroke
Ramipril				
AIRE Acute Infarction Ramipril Efficacy Study (2006) (GOOD)	6-15 months	NNT ~17 (17% vs. 23%, p=0.002)	NNT ~25 for severe or resistant heart failure (10% vs. 14%, p not reported)	NNT ~16 for combined endpoint of mortality, severe/resistant heart failure, reinfarction or stroke (28% vs. 34%, p=0.008), no significant differences for individual outcomes of stroke or reinfarction
Trandolapril				
TRACE Trandolapril Cardiac Evaluation Study (1749) (GOOD)	24 months	NNT ~14 (35% vs. 42%, p=0.001)	NNT ~17 for severe heart failure (14% vs. 20%, p=0.003)	No significant differences for reinfarction

1d. Heart failure

Head-to-head trials. We identified 13 15 head-to-head controlled trials[65-80] of the effectiveness of ACE inhibitors for heart failure (HF) (Evidence Table 9). One trial is described in 2 different publications.[71, 72] There were 10 12 studies of captopril, 2 of cilazapril, 6 of enalapril, 1 fosinopril, 5 lisinopril, 3 quinapril, and 1 ramipril. There were no head-to-head studies of benazepril, trandolapril, moexipril, or perindopril in patients with HF. The number of patients ranged from 13 to 315; 10 trials enrolled fewer than 200 patients. Followup periods ranged from 12 weeks to 12 months, with most (11 of 13) following patients for 12 weeks. Three studies[67, 73, 74] enrolled only patients age 65 and older, and one[71] analyzed a subgroup of patients over age 65 from a larger trial. Most trials enrolled patients with NYHA functional class II or III HF; 2 trials enrolled only more severe patients, with class III to IV HF[68, 78] or LVEF less

than 30%.[75] The majority of patients in all trials were men, and only one trial[72] reported the race or ethnicity of patients.

These trials were fair to poor in quality (Evidence Table 10). Four studies were open-label trials;[67-69, 75] neither patients nor investigators were blinded to treatment assignment. All but 3 trials[67, 68, 75] were multicenter, and the 3 single center trials were open-label. In one trial[73] it is not stated whether patients were randomized to treatment. The method of randomization was described in only 2 trials.[66, 75] No report described the method of allocation concealment used. Seven studies provided information on the source of funding;[67, 70, 72, 73, 75, 77, 78] of these, 7 reported pharmaceutical company support and one[75] reported funding through a grant from the National Heart, Lung, and Blood Institute.

Because there were a large number of head-to-head trials of most ACEIs in patients with heart failure, we only reviewed data from large placebo-controlled trials (discussed in section 1c) and systematic reviews.

Mortality

Only one head-to-head trial reported mortality as a primary outcome.[77] This fair-quality study, conducted in France, compared fosinopril (5mg to 20 mg) to enalapril (also 5 mg to 20 mg) in 254 patients. Recruitment of patients was stratified to enroll at least one-third patients over age 65 (average age was 63). At 12 months of followup, 1.6% of patients randomized to fosinopril had died, compared to 4.6% of those randomized to enalapril (p-value NS, not given). The combined endpoint of total hospitalization plus death was smaller in the fosinopril group (19.7% vs 25.0%, p=0.03). Enalapril was given only once daily in this study, although large placebo controlled trials that showed a reduction in mortality with enalapril used twice-daily dosing[81, 82] and one of these[82] used a higher dose (up to 20 mg twice daily). There are no other head-to-head studies of fosinopril compared with enalapril. Nine other head-to-head trials reported the number of deaths that occurred during the study period (see Evidence Table 9, adverse events column), but mortality was not a primary outcome. No significant differences between ACE inhibitor groups were reported, and the numbers of deaths were too small in these studies to detect any differences if they were present.

The best evidence about the effectiveness of ACE inhibitors on mortality in patients with heart failure comes from five large placebo controlled trials discussed above in Section 1c (recent MI): SAVE (captopril), CONSENSUS (enalapril) SOLVD (enalapril), AIRE (ramipril), and TRACE (trandolapril).

A 1995 meta-analysis evaluated 32 randomized placebo-controlled trials of ACE inhibitors that measured mortality after 8 weeks or longer.[83] Results are reported in Evidence Table 11; most of the studies were small and were not designed to measure mortality as a primary outcome. This study was rated fair quality. Although the method of quality assessment is not reported, the authors conducted a comprehensive search for literature, used explicit criteria for article selection, and provided adequate detail about the primary studies. Studies with at least 8 weeks of followup that reported intention-to-treat results were included.

Eight of 11 ACE inhibitors had data and were included in the meta-analysis: benazepril (2 trials, 233 patients), cilazapril (1 trial, 21 patients), captopril (6 trials, 697 patients), enalapril (7 trials, 3381 patients), lisinopril (4 trials, 546 patients), perindopril (1 trial, 125 patients), quinapril (5 trials, 875 patients), and ramipril (6 trials, 1227 patients). There were no placebo-controlled trials for moexipril, fosinopril, or trandolapril at the time. Overall, there was a

significant reduction in all-cause mortality in patients allocated to an ACE inhibitor (15.8%) compared with placebo (21.9%) (OR, 0.77; 95% CI 0.67-0.88) For the combined endpoint of total mortality or hospitalization, the summary odds ratio was 0.65 (95% CI 0.57-0.74). The evidence for benazepril (2 studies), cilazapril (1 study), and perindopril (1 study) was limited, and results were statistically significant only for enalapril. However, the point estimates for captopril, ramipril, quinapril, and lisinopril were consistent with the summary odds ratio for enalapril (see Evidence Table 11), and there was no heterogeneity of effect among the ACEIs (p=0.87 for total mortality, p=0.88 for mortality plus hospitalization). Results were similar for cause-specific mortality and for trials with longer (>90 days) followup periods, but comparisons among ACE inhibitors were not made for these subanalyses.

In the TRACE trial, discussed above in key question 1c, trandolapril reduced mortality from heart failure in patients with recent MI.

Improvement in NYHA Class

Eleven of 15 head-to-head trials used change in NYHA functional class as an outcome measure (Table 6, below, and Evidence Table 9). In all but one (poor-quality) trial,[69] NYHA class significantly improved over the course of the trial, regardless of which ACE inhibitor patients were taking.

Three studies compared captopril to quinapril, 3 compared captopril to lisinopril, 1 compared captopril to ramipril, 1 compared captopril to cilazapril, 2 compared captopril to enalapril and 2 compared enalapril to lisinopril. In most head-to-head trials, the degree of improvement in NYHA class did not differ between the treatment groups; the ACE inhibitors examined were equally effective in improving functional class. Only 3 studies, [69, 75,67] all poor quality, single-center, open trials, reported a difference between groups in improvement in NYHA class.

Worsening Heart Failure

Only one head-to-head trial[77] reports hospitalization for deteriorating HF, the same trial that reported mortality. Event-free survival time was longer in the fosinopril group versus the enalapril group at doses of 5 to 20 mg daily. As noted in the mortality discussion above, these results may be due to an inadequate dose of enalapril given in the control group.

Five head-to-head trials reported deterioration in NYHA Class as an outcome. There were 3 comparisons of captopril versus lisinopril,[66, 72, 74] 1 comparison of captopril versus quinapril,[67] and 1 study of fosinopril versus .enalapril.[76] Two studies, both comparing captopril to lisinopril, were fair quality,[72, 74] and both found no significant difference between groups in the proportion of patients who deteriorated based on the ACE inhibitor to which they were assigned.

Table 6. Head-to-head trials of ACEIs in patients with heart failure

Study	N	Comparison	Length of follow-up	Improvement in NYHA Class	Quality Rating
Packer 1986	42	Captopril vs Enalapril	12 weeks	71% vs 52%	Poor
Dirksen 1991	40	Enalapril vs Captopril	12 weeks	Improvement from baseline statistically significant (p=0.02) only in enalapril group Improvement by at least 1 class: 37% vs 33% (p not reported)	Poor
Haffner 1995	80	Captopril vs Enalapril	6 months	Not reported	Poor
Cilazapril-Captopril Group 1995	329	Cilazapril vs Captopril	6 months	Improvement by at least one class: 35% vs 36% (NS); also NS vs placebo (32%)	Fair
Bach 1992	287	Lisinopril vs Captopril	12 weeks	35% vs 40% (p-values not reported)	Poor
Giles 1988, 1989	65	Lisinopril vs Captopril	12 weeks	30% vs 31% improved (p=NS) Subgroup of patients over age 65 (Giles 1988): 24% vs 26% improved (p not reported)	Fair
Morisco 1997	251	Lisinopril vs Captopril	12 weeks	37.8% vs 36.9% changes similar in both groups (no p-values reported).	Fair
Zannad 1992	278	Lisinopril vs Enalapril	12 weeks	48% vs 43%(p= NS)	Poor
Zebrah Study Group (Adgey) 1993	251	Lisinopril vs Enalapril	6 months	Improvement by one or more class: 68% vs 70% (p=NS)	Fair
Gavazzi 1994	146	Quinapril vs Captopril	12 weeks	Improvement in NYHA class 27.1% vs 24.0% (NS)	Fair
Beynon 1997	61	Captopril vs Quinapril	16 weeks after 2 to 8 weeks titration	10% vs 17% (p=0.02)	Poor
Acanfora 1997	121	Quinapril vs Captopril	12 weeks	NYHA Class at Week 12: Class I 8% vs 3% (p=NS) Class II 86% vs 75% (p=NS) Class III 6% vs 22% (p<0.05)	Fair
de Graeff 1989	13	Ramipril vs Captopril	12 weeks	58% vs 40% (p-value not reported)	Poor

Exercise Duration

Five head-to-head studies [65, 66, 71, 72, 76, 80] (two comparing captopril to lisinopril, one comparing captopril to quinapril, one comparing enalapril to fosinopril, and one comparing cilazapril to captopril) measured increase in exercise duration as an outcome, and 2 others (1 comparing captopril to enalapril and 1 comparing captopril to quinapril) measured increase in distance during a 6-minute walking test.[67, 73] Four of these were rated fair quality and the rest were poor.[65, 71, 72, 76, 80]

A 12-week study that enrolled 131 patients[65] found no difference in increase in exercise duration in patients taking quinapril compared with captopril (7.8 $\pm$ 1.9 seconds vs 7.1 $\pm$ 2.3 seconds, p=NS). Thirty-two percent of patients taking quinapril stopped the exercise test due to fatigue, compared with 26% of those taking captopril (p=NS).

Another study of 189 patients with HF Class II-IV,[72] no difference in the mean increase in exercise duration at week 12 in patients assigned to take lisinopril versus those assigned to captopril. In a subgroup of 65 patients over age 65,[71] there was a greater increase in exercise duration in patients taking Lisinopril (134.3 seconds vs 71.8 seconds, p=0.08).

In a study that compared lisinopril with enalapril in 278 patients for 12 weeks,[76] patients in the lisinopril group increased their exercise duration by 65.1 seconds, compared with 41.9 seconds for the enalapril group (p=0.07). Before the run-in period, patients in the Lisinopril group had a lower mean exercise capacity, although the difference was not significant at the end of the run-in period. This study did not use an intention-to-treat analysis; only those who completed the study were analyzed. As in the other study that showed a difference in exercise duration, there was no difference between the groups in NYHA class.

The trial of cilazapril versus captopril[80] found no difference in duration of exercise testing at 24 weeks between the two treatment groups.

Quality of Life

A placebo-controlled, head-to-head trial of cilazapril versus captopril [79] focused on quality of life (Evidence Table 9). On four different measures (sickness impact profile, profile of mood states, Mahler index of dyspnea-fatigue, and a health status index), there was a small improvement in quality of life after 24 weeks for both ACEI groups, but no difference between the two treatment groups. There was more improvement in ACEI groups than placebo, but the difference was not statistically significant.

1e. Diabetic and nondiabetic nephropathy

ACEIs are used in patients with diabetes who have evidence of renal disease to prevent its progression and in patients with diabetes who have no evidence of renal disease to prevent the development of renal disease. Our searches identified over 300 publications that addressed renal disease in diabetes. However, we did not identify any head-to-head trials of ACEIs in patients with diabetic nephropathy.

ACEIs reduce or eliminate microalbuminuria, an early sign of renal damage in patients with diabetes (and those without).[84] They have also been used in patients who have frank proteinuria (> 3 gm/d) and in patients who have decreased renal function.

Type 1 Diabetes. The Collaborative Study Group trial of captopril in 409 patients with Type 1 diabetes was the first study to demonstrate that an ACEI can reduce the incidence of advanced renal failure.[85] On average, the subjects had diabetes for 22 years and had close to 3gms of proteinuria a day. The average HgbA1c was 11.7% and three-quarters had hypertension. The maximum followup period was 3 years. In this trial, compared with placebo, captopril reduced the risk of doubling of serum creatinine (NNT 10, p=0.007) and reduced the combined endpoint of death, dialysis, or transplant to a similar degree (NNT 10). The study was well-conducted, but its dramatic results apply to a small proportion of patients with diabetes—those with longstanding, poorly controlled Type 1 diabetes, most of whom had hypertension and significant proteinuria.

Subsequently, the European Microalbuminuria Captopril Study Group[86] and the North American Microalbuminuria Study Group[87] demonstrated that, in patients with Type 1 diabetes with microalbuminuria and without hypertension, captopril prevented the onset of clinical proteinuria and hypertension. In the NAMSG trial, creatinine clearance stayed stable in the captopril group but decreased by 10 ml/min over 2 years in the placebo group. Neither study demonstrated an effect on the risk of developing end-stage renal disease.

Lisinopril[88] and perindopril[89] also reduce urinary albumin excretion, but have not been shown to prevent the development of renal failure in patients with Type 1 diabetes. Enalapril was equivalent to placebo and to nifedipine in a 3-year trial in normotensive patients with Type 1 diabetes who had microalbuminuria.[90] Initially, enalapril improved urinary albumin excretion, but by 3 years there was no effect on this measure or on the development of hypertension.

Noninsulin-dependent diabetes. While ACEIs reduce albuminuria in normotensive patients with non-insulin dependent diabetes and microalbuminuria,[91-96] they have not been shown to prevent the development of end-stage renal disease in this group.[97 31]

Prevention of diabetes. Post-hoc analyses from SOLVD (enalapril) and from HOPE (ramipril) provide strong evidence that ACEIs delay or prevent the development of diabetes, particularly in patients who have glucose intolerance.[98, 99]

Renal insufficiency or renal disease without hypertension. In a trial of 583 patients with renal insufficiency from various causes, benazepril reduced the risk of developing end-stage renal disease or a doubling of serum creatinine by approximately fifty percent.[100] At baseline, renal insufficiency was mild in 39% of all patients, and moderate in 61%. Only 21% of the subjects had diabetic nephropathy, but the effect was stronger in this subgroup than in the sample as a whole. There was only one death in the placebo group (0.4%), compared with 8 in the benazepril group (2.7%; p=0.04). The authors state that it is not clear why there were more deaths in the benazapril group, and note that the overall number of deaths from cardiac causes was low in comparison with mortality from cardiovascular disease reported in studies of similar patients.

Key Question 2: For adult patients, do angiotensin converting enzyme inhibitors differ in safety or adverse events?

Adverse effects of ACEIs include hypotension, dry cough, angioedema, hyperkalemia, and acute renal impairment. Other adverse effects include rashes, hepatotoxicity, dysgeusia (i.e.,

distortions of taste), and neutropenia. The last two of these—loss of taste and neutropenia—were seen primarily with the use of high doses of captopril (e.g., >100 mg/day). Heart failure, and interactions with medicines used in heart failure, are considered to increase the risk of hypotension and acute renal impairment from ACEIs.

Angioedema (also called angioneurotic edema) is a nonpitting edema, usually involving the face, lips, tongue, or larynx, but sometimes observed in the GI tract. It is usually mild, but in severe cases it is treated with intravenous antihistamines and airway management. In a large trial of enalapril versus placebo, ACEI use increases the risk of angioedema 4-fold, from 1 per 1,000 to 4 per 1,000 among all subjects.[101] The same increase was seen in the ALLHAT study: the rate was 4 per 1,000 for lisinopril users, versus <1 per 1,000 for the other treatments.[12] In the HOPE trial, the rate of angioedema was 2 per 1,000 in the placebo group and 4 per 1,000 for ramipril users.[30]

Head-to-head trials. Twenty-four head-to-head trials compared the rates of adverse events from ACEIs available in the U.S. Nine of these concerned patients with hypertension, two concerned recent MI patients, and 13 concerned patients with heart failure.

Hypertension

Two of the head-to-head trials focused on quality of life; these were described in section 1A above.[23, 24] In the remaining studies, there were no important differences in the rates of cough, angioedema, hyperkalemia, or acute renal impairment.[102-108]

Recent MI

In the two head-to-head trials (Evidence Table 12), adverse event assessment was rated fair quality.[37, 38] The quality of adverse event assessment in these two trials was lower than the quality for general internal validity (Evidence Table 4). In both trials, adverse event assessment methods were not adequately described, adverse events were not specified or pre-defined, and potential confounders were not evaluated.

Withdrawals due to adverse events were not specifically reported in either trial. Although neither study found significant differences between different ACEIs for overall withdrawals, each study reported more overall withdrawals in the group receiving captopril. In one trial, the overall withdrawal rate was 24% for captopril vs. 16% for enalapril,[37] and in the other trial, 14% for captopril vs. 9% for perindopril.[38] Neither trial reported significantly different adverse event rates for cough or symptomatic hypotension. Permanent increases in renal function were not reported in either trial. Reliable conclusions about differential safety or adverse event rates could not be drawn from head-to-head trials.

Heart failure

Evidence Table 13 shows the adverse events reported in head-to-head trials. Only one head-to-head trial was specifically designed to assess adverse events.[75] In this small (N=42), poor-quality, fixed-dose, open trial, 10% of patients taking enalapril 20 mg twice daily had first dose hypotension, and 5% had serious hypotension after 6 weeks of treatment, compared with no

hypotension in patients taking captopril 50 mg three times daily. There were no withdrawals due to any adverse effects in this 12-week study, including hypotension.

In 15 head-to-head trials, the percentage of patients who withdrew due to adverse events ranged from none to 39%, and differed between groups in only one (cilazapril 5.4% vs captopril 13.0%, p-value not reported).[80] Ten studies[67-76, 80] reported the number of withdrawals due to hypotension (first dose or not), and the percentages were low in most (0%-3%). The exception was one study[73] that reported 10% withdrawals due to hypotension in the enalapril (2.5 mg twice daily) group compared with 0 in the captopril (12.5 mg twice daily) group. Doses were not titrated in this study, which may account for the high rate of hypotension.

Another study[77] reported a significantly higher occurrence of symptomatic orthostatic hypotension in patients taking enalapril 5 to 20 mg once daily compared to those randomized to fosinopril 5 to 20 mg once daily (7.6% vs 1.6%). There were no withdrawals due to hypotension in this study, and the overall withdrawal rate was similar between groups.

Six trials[65, 66, 68, 71-74] reported the number of deaths that occurred during the treatment period. There were no significant differences in the number of deaths between groups in any of these.

Placebo-controlled trials. In 12 large placebo-controlled trials of ACEIs in patients with recent myocardial infarction, adverse event assessment was fair or poor (Evidence Table 7). In general, trials did not adequately report adverse event assessment techniques or predefine adverse events. The most consistently reported adverse event was hypotension, but definitions of 'significant' hypotension varied widely between studies. Rates of hypotension varied widely. For example, for captopril, rates of hypotension ranged from 8% to 37% in different trials. No clear pattern of one ACEI being superior to another for this adverse event could be seen in the data from these trials. Other adverse events (including cough, angioedema, significant renal failure, and withdrawal due to adverse events) were inconsistently reported, and no reliable conclusions could be drawn from these data.

A recent meta-analysis examined adverse events in 51 placebo- or standard treatment-controlled randomized trials of ACE inhibitors in patients with heart failure or ventricular dysfunction.[109] A total of 18,234 patients were studied in trials with at least 8 weeks of followup. The withdrawal rate was 24.3% in patients randomized to ACE inhibitors versus 27.8% in those allocated to reference treatment. Percentages of patients who withdrew due to worsening heart failure were 6.3% for ACE inhibitors and 11.7% in control groups (RR= 0.54; 95% CI 0.46-0.63). Excluding withdrawals due to MI and hypertension, withdrawals due to adverse events were 13.8% for ACE inhibitors and 9.4% for control groups (RR=1.54, 95% CI 1.30-1.83); for every 32 patients treated with an ACE inhibitor, one additional treatment withdrawal due to an adverse event occurred. Although adverse event rates for individual ACE inhibitors were not reported, there was no heterogeneity among the trials regarding withdrawals due to adverse events related to ACE inhibitors (p=0.14).

Observational studies. We identified no large, good-quality community-based or population-based observational studies designed to assess comparative safety of different ACE inhibitors. A large, fair-quality observational study conducted in multiple general practices in Germany[110] included 33,841 patients who were prescribed cilazapril. Patients were followed for an average of 109 days. At each check up patients were asked if they had experienced any adverse events. Adverse events were reported by 7.3% of patients during treatment, 6.7% of all

patients discontinued treatment, and 3.8% of the study population discontinued due to adverse events. Forty-four patients died during the study (12 cardiac events, 10 cerebral events, 3 pneumonia, 2 accidents, 4 malignancies, 13 cause unknown). Dry cough was reported in 1.5% of all patients, and led to discontinuation of treatment in 1.1%.

Key Question 3: Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one angiotensin converting enzyme inhibitor is more effective or associated with fewer adverse events?

No data suggest that one ACEI is better than others for demographic subgroups (age, race, gender). Although the recommended initial dose of trandolapril is higher in African American than in white patients, we found no data suggesting its efficacy is different from other ACEIs.

A 1995 fair-quality meta-analysis of placebo-controlled trials of ACEIs in heart failure found no difference in total mortality or hospitalization in subgroups based on age, sex, NYHA Class, or etiology.[83] A more recent meta-analysis of the seven largest placebo-controlled trials of ACEIs (CONSENSUS, SAVE, SOLVD Prevention, SOLVD Treatment, SMILE, TRACE, AND AIRE) made 3 comparisons: African Americans vs. whites, men vs. women, and patients with diabetes vs. those without diabetes.[111] Its findings are summarized in Table 7 below.

Table 7. Results of meta-analysis by race, gender, and diabetes

Group of Interest	Number of Studies (Patients in group of interest)	RR for Mortality for Group of Interest (95% CI)	RR for Mortality for Other Subjects (95% CI)
African Americans	2 (800)	0.89 (0.74-1.06)	0.89 (0.82-0.97)
Women	6 (2,373)	0.92 (0.81-1.04)	0.82 (0.74-0.90)
Patients with diabetes	6 (2,398)	0.84 (0.70-1.00)	0.85 (0.78-0.92)

From Shekelle et al, 2003[111]

In patients with diabetes and in African Americans, the effects of ACEIs were similar to those in the general population. However, women seemed to benefit less than men. The lack of effect in women was especially pronounced in studies that enrolled patients with *asymptomatic* LV dysfunction (RR Female 0.96, 95% CI 0.75-1.22; vs. for RR Female 0.90, 95% CI 0.78-1.05 for *symptomatic* HF). In men the effect was similar in patients with symptomatic and asymptomatic LV dysfunction.

ACEIs appear to have more beneficial effects in recent myocardial infarction patients at higher risk for recurrent cardiovascular events (patients with heart failure, diabetes, or hypertension), but no single ACEI has been found to be superior for any of these conditions.[58, 64, 112-118]

Patients with renal insufficiency or renal disease. Trials in patients with recent MI generally excluded patients with renal disease. There are no data from head-to-head trials about the comparative efficacy of different ACEIs in patients with recent myocardial infarction and renal insufficiency.

Similarly, there is little information about ACEIs in patients with heart failure and renal insufficiency. Most trials either excluded patients with renal disease, or did not perform a subgroup analysis of patients with renal insufficiency.[119] CONSENSUS, a placebo-controlled trial of enalapril in patients with severe heart failure, included patients with moderate renal insufficiency (median serum creatinine level 1.4 mg/dL). Overall, patients in the enalapril group had 31% lower mortality at 1 year, and those with baseline serum creatinine levels greater than and less than the median had similar survival benefit. There are no data from head-to-head trials about the comparative efficacy of different ACEIs in patients with heart failure and renal insufficiency.

African Americans. At present, the role of ACEIs in the management of hypertension, recent myocardial infarction, and heart failure, and patients with kidney disease is the same for African Americans and others. In head-to-head trials, there are no data to suggest that one ACE inhibitor is superior to another in African American patients.

One trial enrolled only African Americans. The AASK trial (see Table 3, above) compared an ACEI, a beta blocker, and a calcium channel blocker in African Americans with hypertensive kidney damage. The primary outcome measure was reduction in GFR by 50% or more (or > or =25 mL/min per 1.73 m2) from baseline, ESRD, or death. Compared with the metoprolol and amlodipine groups, the ramipril group manifested risk reductions in this clinical composite outcome measure of 22% (95% CI, 1%-38%; P =.04) and 38% (95% CI, 14%-56%; P =.004), respectively.[19]

AASK did not include a diuretic as one of the treatments. In ALLHAT, which enrolled hypertensive patients who did not have the advanced kidney damage of the AASK patients, a diuretic was better than an ACEI (lisinopril) for preventing cardiovascular events in all races.[12] This was especially true for African Americans: rates of stroke were 40% higher in the lisinopril group compared with the chlorthalidone group for African Americans, with no difference in other patients; rates of the combined CVD endpoint were 19 percent higher in African Americans taking lisinopril versus chlorthalidone compared to a 6 percent increased rate in other patients.

African American patients who take ACEIs are at higher risk of developing angioedema, a complication of ACEI therapy, than other Americans. The risk is two[12] to four times[120] as high in African-Americans ACEI users as in other American users. In the AASK trial, the rates of angioedema over 3.5 to 6 years of followup were 6.4% for ramipril, versus 2.3% and 2.7% for the other drugs ($p<0.05$ for both comparisons). There is currently no evidence that one ACEI is safer than others for African American patients.

Elderly. One fair quality head-to-head trial of lisinopril 5 mg to 20 mg once daily versus captopril 12.5 mg to 50 mg three times daily analyzed a subgroup of 65 patients over age 65.[71] There was no difference between treatment groups in change in NYHA class after 12 weeks of treatment. Increase in exercise duration was slightly, but not significantly, higher in the captopril group (134.3 vs 71.8 seconds, $p=0.08$). A second fair-quality trial [74] of lisinopril versus captopril in patients ages 65 to 80 also found no difference in change in NYHA class after 12 weeks.

Other drugs. ACEIs appear to be effective when used with nitrates,[56, 57] aspirin,[121] thrombolytics,[50] and other agents conventionally used to treat myocardial infarction, but there are no data regarding comparative efficacy or safety in patients on these medications. Many trials

excluded patients with severe hypotension or renal failure, and we found no data to suggest that one ACEI is superior to others for patients with these conditions. Theoretically, an ACEI with a shorter half-life (captopril) may be safer in patients at risk for severe hypotension or acute renal failure, but we found no trials comparing the safety of captopril versus longer-acting ACEIs in these patients.

Summary

Tables 8 and 9 summarize the results of this review. There is evidence from head-to-head trials that, especially in heart failure, many ACEIs are similar in short-term effectiveness and adverse events. Several ACEIs reduce mortality after MI in various subgroups (no HF, asymptomatic LV dysfunction, and clinical HF). There is no definitive evidence that they differ in long-term effectiveness for major cardiovascular and renal endpoints. Across indications, the evidence for mortality reductions is strongest for captopril, enalapril, and ramipril.

Table 8. Outcomes data for ACEIs							
Drug	**Hypertension without compelling indications**	**Hypertension plus Diabetes**	**History of CVD or High cardiac risk**	**Recent myocardial infarction**	**Heart Failure**	**Diabetic Nephropathy**	**Other nephropathy**
Benazepril					Reduced mortality and hospitalization in 2 small placebo-controlled studies.	Reduced ESRD/death in patients with renal disease, 21% had diabetes.	
Captopril	=diuretic, beta blocker for composite of MI, stroke, CV deaths	= beta blocker for macrovascular and microvascular outcomes		Consistently reduced mortality and heart failure in several trials	Improved functional outcomes in head-to-head trials. Reduced mortality in placebo-controlled studies.	Reduced ESRD/death and onset of hypertension in patients with Type I diabetes.	
Cilazapril					Improved functional outcomes in head-to-head trials.		
Enalapril	> diuretic for CV events	> CCB for CV events	Reduced major CV events	>captopril in a small head-to-head trial, but placebo-controlled studies had inconsistent results	Improved functional outcomes in head-to-head trials. Reduced mortality in placebo-controlled studies.		
Fosinopril		> CCB for composite of MI, stroke, or hospitalized angina		1 small trial, reduced heart failure but no mortality benefit	vs. enalapril, NS trend toward lower mortality. Improved functional outcomes in head-to-head trials.		
Lisinopril	< diuretic for CV events			reduced mortality at 6 months in a large, good-quality trial	Improved functional outcomes in head-to-head trials. Reduced mortality and hospitalization in 3 small placebo-controlled studies.		

Table 8. Outcomes data for ACEIs (continued)							
Drug	**Hypertension without compelling indications**	**Hypertension plus Diabetes**	**History of CVD or High cardiac risk**	**Recent myocardial infarction**	**Heart Failure**	**Diabetic Nephropathy**	**Other nephropathy**
Moexipril							
Perindopril			Reduced CV events but no difference in overall mortality in 1 large placebo controlled trial. No difference from placebo in 1 trial	= captopril for mortality and revascularization rates in one small head-to-head trial	Non-significant reduction in mortality in one small placebo-controlled trial.		
Quinapril			No difference from placebo in 1 trial		Improved functional outcomes in head-to-head trials.	Reduced mortality in placebo-controlled studies.	
Ramipril			Reduced all-cause mortality and major CV events in 1 study; non-significant trend in another study.	Reduced mortality and heart failure in a large, good-quality trial	Improved functional outcomes in head-to-head trials. Reduced mortality in placebo-controlled studies.		Reduced ESRD/death in African Americans with hypertensive renal disease and in patients without diabetes with renal disease.
Trandolapril				Reduced mortality and heart failure in a large, good-quality trial	Reduced mortality in a large, good-quality trial		

CCB= calcium channel blocker, ESRD=end-stage renal disease or doubling of creatinine.

Table 9. Summary of evidence

Comparative efficacy	Overall grade of evidence for distinguishing among ACEIs **	Conclusion
Key question 1:		
a. Hypertension	Good for quality of life	Long-term quality of life was better with captopril than with enalapril in men without compelling indications.
	Poor for other long-term health outcomes	No other outcomes assessed in head-to-head trials. For patients without diabetes, ACEIs are less effective than diuretics. There are no data to suggest that one ACEI is superior to others for hypertension without "compelling indications."
b. High cardiovascular risk factors	Fair	There are no head-to-head trials. In patients who have a history of coronary disease with or without hypertension, and other patients at high risk of CAD, ramipril is the only ACEI to reduce all-cause mortality (NNT 56). Enalapril, perindopril, and ramipril reduced major cardiovascular events in patients with CAD.
c. Recent myocardial infarction	Fair	1 fair-quality head-to-head trial (Foy 1994) of captopril vs. enalapril found a significant difference in mortality (12% vs. 1%) but this was a relatively small trial (n=225). Another fair-quality head-to-head trial (Lau 2002) found no significant differences for mortality or revascularization rates for captopril vs. perindopril. No other head-to-head trials of included ACE-I's was available. Captopril, lisinopril (6-months), ramipril, and trandolapril reduced mortality and heart failure in good-quality, placebo-controlled trials. Enalapril had a slight trend towards increased mortality in a large, good-quality placebo-controlled trial, but significantly reduced the rate of heart failure requiring hospitalization. In a smaller placebo-controlled trial, there was a trend towards increased mortality and decreased heart failure on fosinopril. 2 systematic reviews were not designed to assess comparative efficacy.

Table 9. Summary of evidence (continued)

Comparative efficacy	Overall Grade of Evidence**	Conclusion
Key question 1 (continued):		
d. Heart failure	Good for functional outcomes Fair for mortality and major CV events.	1 fair-quality head-to-head trial showed no difference in total mortality between fosinopril vs enalapril. Decreased hospitalization plus mortality in fosinopril group may have been due to dosing schedule. 1 fair-quality meta-analysis of 32 placebo controlled trials showed no heterogeneity of effect for mortality or mortality plus hospitalization among benazepril, captopril, cilazapril, enalapril, lisinopril, perindopril, quinapril, and ramipril, with most evidence from trials of captopril, enalapril, ramipril, quinapril, and lisinopril, and limited evidence for benazepril (2 studies), cilazapril (1 study), and perindopril (1 study) was limited, In 15 head-to-head trials there was no difference in improvement in NYHA class or exercise duration for captopril, enalapril, fosinopril, lisinopril, quinapril, and ramipril. There are no head-to-head trials of benazepril, trandolapril, moexipril, or perindopril, and no placebo-controlled trials of moexipril.
e. Diabetic and nondiabetic nephropathy	Poor	There are no head-to-head trials. Captopril reduced ESRD and death, but only in patients with longstanding Type 1 diabetes. Several ACEIs reduce proteinuria in patients with diabetes. Benazepril reduced end-stage renal disease and doubling of creatinine in one placebo controlled trial of patients with renal insufficiency from various causes and no hypertension. Effect was stronger in the subgroup with diabetic nephropathy. Ramipril reduced ESRD/death in African Americans with hypertensive renal disease and in patients without diabetes with renal disease.
Comparative safety		
Key question 2:		
General	Poor	There is no evidence that any ACEI is associated with a lower risk of serious complications than other ACEIs.
For specific indications		
Recent myocardial infarction	Fair/Poor	Adverse event assessment quality was generally worse than quality for assessing clinical efficacy. 2 head-to-head trials provided inconclusive evidence regarding comparative efficacy. Placebo-controlled trials provided no additional data.
Heart failure	Fair	No good or fair quality head-to-head trial was designed to assess safety. Withdrawals due to adverse effects did not differ in 9 head-to-head trials. A meta-analysis of 51 placebo-controlled trials found no heterogeneity of effect among ACE inhibitors. There are no head-to-head trials of benazepril, trandolapril, moexipril, or perindopril, and no placebo-controlled trials of fosinopril, moexipril, or trandolapril.

Table 9. Summary of evidence (continued)

Comparative efficacy	Overall Grade of Evidence**	Conclusion
Subgroups		
Key question 3:		
Women	Poor	For heart failure, ACEIs may be less effective in women. There are no data on how different ACEIs compare in women.
African Americans	Fair	ACEIs are as effective in African Americans as in others. There are no data on how different ACEIs compare in African Americans.
Elderly patients	Fair	In 2 fair quality trials of lisinopril vs captopril for heart failure in elderly patients, there was no evidence that one was more effective than another. A meta-analysis of 32 trials found no differences among ACEIs based on age.

** based on criteria developed by the US Preventive Services Task Force.

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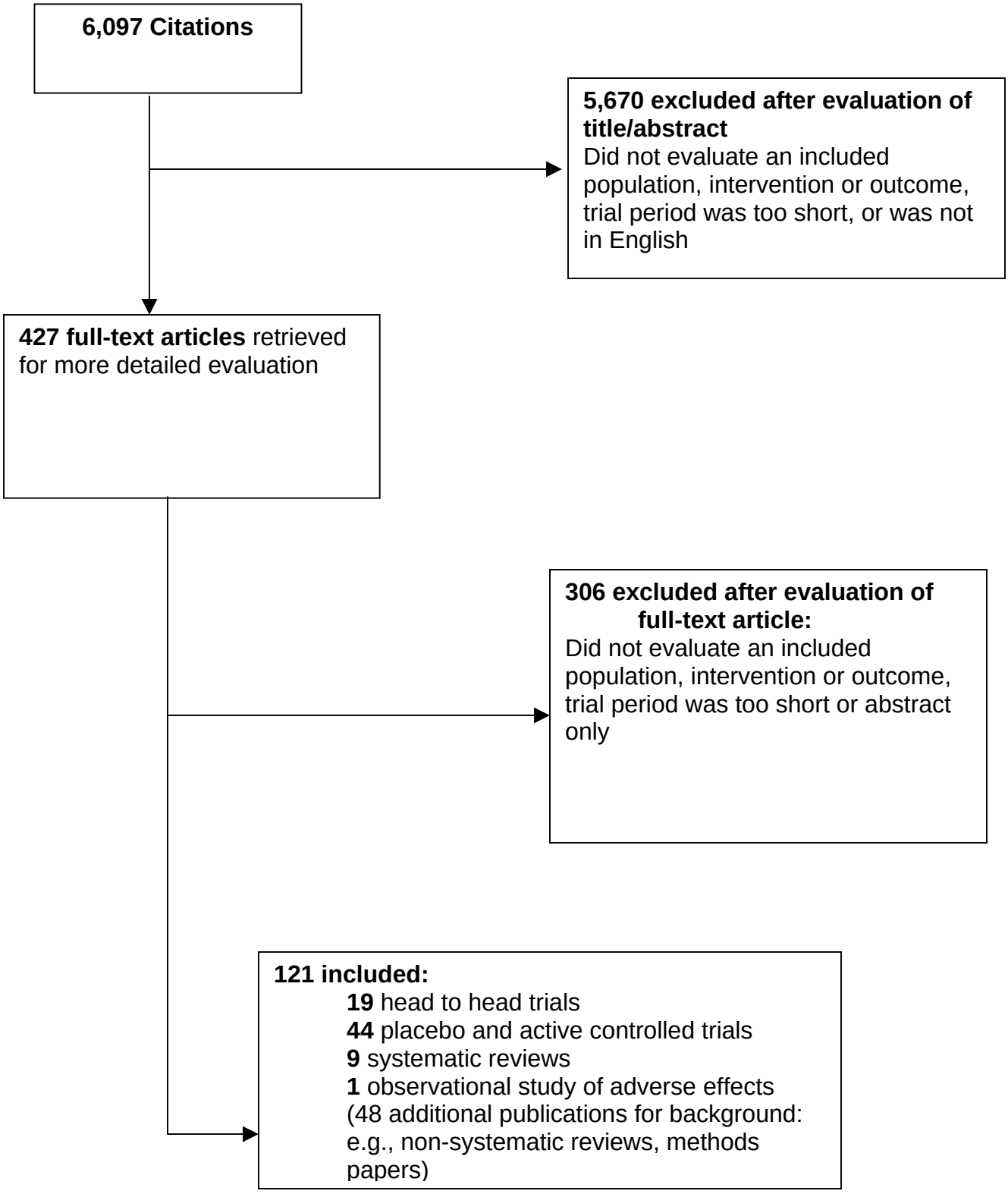
Figure 1: ACE Inhibitors drug class review flow diagram



Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)
EUROPA Investigators, 2003 Multiple European countries EUROPA Study (FAIR)	Multicenter	At least 18 years old without clinical evidence of heart failure and with evidence of coronary heart disease, documented by previous MI (>3 months prior), percutaneous or surgical coronary revascularization (>6 months prior), or angiographic evidence of at least 70% narrowing of one or more major coronary arteries. Men could also be recruited if they had a history of chest pain and a positive EKG, echo, or nuclear stress test.	Perindopril 8 mg. Reduced to 4 mg if not tolerated.
HOPE Study Investigators, 2000 Mann 2003 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial (FAIR)	2 X 2 factorial design (vitamin E and ramipril) Multicenter	At least 55 years old with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol, low HDL-C, cigarette smoking, or documented microalbuminuria.	Ramipril 10 mg

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Run-in/Washout	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
EUROPA Investigators, 2003 Multiple European countries EUROPA Study (FAIR)	4 week run-in: patients received 4 mg perindopril once daily for 2 weeks in addition to their normal medicaiton, followed by 8 mg perindopril for 2 weeks if the lower dose was well tolerated. Patients aged 70 or older were given 2 mg perindopril in the first week, followed by 4 mg in the second week, and 8 mg in the last 2 weeks. Excluded from randomization if hypotension, raised potassium or creatinine concentratins, other intolerance, major clinical events, poor adherence to treatment, exclusion or non-inclusion criteria, withrawn consent, unsepecified stop reason, and patients never randomized.	Yes (lipid lowering drugs, beta blockers, calcium channel blockers)	Primary endpoint: composite of cardiovascular death, non-fatal MI, and cardiac arrest with successful resuscitation. Initially, the primary endpoint was defined as the composite of total mortality, non-fatal MI, unstable angina, and cardiac arrest with successful resuscitation. Primary endpoint was changed towards the end of the initial proposed followup period. Mean 4.2 years followup. Followup was originally to be 3 years. At the end of 3 years, the definition of primary endpoint was changed and study was extended by one year.
HOPE Study Investigators, 2000 Mann 2003 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial (FAIR)	In run-in, all patients received 2.5 mg ramipril for 7 to 10 days followed by matching placebo for 10 to 14 days. Excluded from randomization for noncompliance, side effects, abnormal serum creatinine or potassium levels, or withdrawal of consent.	All patients received vitamin E or placebo vitamin E. Other medications not reported.	Primary outcome: composite of myocardial infarction, stroke, or death from cardiovascular causes. Followup 5 years. Secondary outcome: Development of renal disease over 4.5 years (n=7674)

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
EUROPA Investigators, 2003 Multiple European countries EUROPA Study (FAIR)	Mean age 60 years (SD 9) 85% male ethnicity not reported	65% previous MI, 55% previous revascularization, 12% diabetes, 27% hypertension, 63% hypercholesterolemia.	# screened not reported/13,655 eligible/12,218 enrolled after run-in	2657 withdrawn/3 lost to followup/12,215 analyzed
HOPE Study Investigators, 2000 Mann 2003 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial (FAIR)	Mean age 66 years (SD 7) 73.3% male ethnicity not reported	History of CVD (80%) or diabetes (38%) plus one other risk factor (HTN—47%, High cholesterol—66%, smoking—14%). Patients with nephropathy or heart failure were excluded.	# screened not reported/#eligible not reported/9,297 enrolled	# withdrawn not reported/# lost to followup not reported/9,297 analyzed

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals/withdrawals due to adverse events
EUROPA Investigators, 2003 Multiple European countries EUROPA Study (FAIR)	CV events (cardiovascular death, non-fatal MI, cardiac arrest with successful resuscitation) at (mean followup) 4.2 years NNT=50 RR 0.80 (0.71-0.91) All-cause mortality at 4.2 years RR=0.89 (0.77-1.02)	Not reported	"specific adverse effects, such as cough, hypotension, or abnormal creatinine rise were infrequent."	Total withdrawals not reported ('withdrawals from treatment were similar to those for placebo'); withdrawals for cough 2.7% perindopril vs 0.5% placebo.
HOPE Study Investigators, 2000 Mann 2003 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial (FAIR)	CV events at 5 years: NNT 26.7 RR 0.79 (0.72-0.86) All-cause mortality at 5 years: NNT 56 RR 0.84 (0.75-0.95) Development of Renal Disease at 4.5 years:	"Serious adverse events are recorded."	cough, hypotension or dizziness, angioedema were reasons for withdrawal.	ramipril vs placebo: 28.9% vs 27.3% withdrew overall 7.3% vs 1.8% withdrew due to cough 1.9% vs 1.5% withdrew due to hypotension or dizziness 0.4% vs 0.2% withdrew due to angioedema.

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)
Marre et al. 2004 Multiple European countries DIABHYCAR Study (FAIR)	Multicenter	Over age 50 with type 2 diabetes (defined on the basis of receiving current treatment with at least one oral antidiabetic agent), urinary albumin excretion 20 mg/l or higher in 2 successive random urine samples.	Ramipril 1.25 mg once daily.
MacMahon, 2000 Australia and New Zealand PART2 Trial (FAIR)	Multicenter	Age 75 or younger with a hospital diagnosis (within 5 years of enrollment) of any of the following: acute MI, angina with coronary disease confirmed by angiograpy or exercise EKG, transient ischemic attack or intermittent claudication.	Ramipril 5-10 mg
Pitt, 2001 US, Canada, Europe QUIET Study (FAIR)	Multicenter	18 to 75 years of age, had undergone successful coronary angioplasty or atherectomy at baseline, and had at least 1 coronary that had not been subjected to mechanical revascularization.	Quinapril 20 mg

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Run-in/Washout	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Marre et al. 2004 Multiple European countries DIABHYCAR Study (FAIR)	Not reported	Usual treatment; ~47.5% were using antihypertensive agents, ~ 28% lipid lowering agents, ~18.5% antiplatelets.	Primary endpoint: combined incidence of cardiovascular death (including sudden death), non-fatal acute MI, stroke, heart failure requiring admission to hospital, and end stage renal failure (defined as requirement for hemodialysis or kidney transplant). Investigators examined participants every six months for at least 3 years.
MacMahon, 2000 Australia and New Zealand PART2 Trial (FAIR)	2-week run-in in which patients received ramipril 5 mg daily for the first week and ramipril 10 mg daily for the second week. Compliant patietns who tolerated at least 5 mg ramipril daily were randomized.	Not reported	Primary outcome measures were ultrasound recordings of the carotid arteries and echocardiograms. Details of all clinical events resulting in death, hospitalization, or withdrawal from study treatment were also recorded throughout followup. Followup 4 years.
Pitt, 2001 US, Canada, Europe QUIET Study (FAIR)	None	Excluded calcium channel blockers and lipid-lowering agents; subset of 453 randomly selected patients underwent repeat coronary angioplasty.	Occurrence of 1 of the following cardiac events: cardiac death, resuscitated cardiac arrest, nonfatal MI, coronary artery bypass graft surgery, coronary angioplasty, or hospitalization for angina pectoris. Primary outcome was time to first cardiac event. Followup 2 years

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Marre et al. 2004 Multiple European countries DIABHYCAR Study (FAIR)	Mean age 65 (SD 8) 70% male ethnicity not reported	56% hypertensive ((>140/90 mm Hg and taking antihypertensive drugs), 73%-74% microalbuminuria, 26% proteinuria, 77.6% ramipril and 73.6% placebo had no previous cardiovascular disease	25,468 screened/5,948 eligible/4,937enrolled	678 dropped out/160 lost to followup/4912 analyzed (25 withdrawn due to major misconduct by investigator were withdrawn after randomization)
MacMahon, 2000 Australia and New Zealand PART2 Trial (FAIR)	Mean age 61 82% male Ethnicity not given	Medical history (ramipril vs placebo): MI 43% vs 41% Angina 66% vs 65% Peripheral vascular disease 20% vs 20% TIA or stroke 11% vs 9% Type I diabetes 2% vs 3% Type II diabetes 6% vs 6%	# screened not reported/744 eligible/617 enrolled after run-in	Not reported
Pitt, 2001 US, Canada, Europe QUIET Study (FAIR)	Mean age 58 years 82% male 94% white	History of PTCA, normal lipid levels	# screened not reported/# eligible not reported/1,750 enrolled	464 withdrew/4 lost to followup/1,750 analyzed

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals/withdrawals due to adverse events
Marre et al. 2004 Multiple European countries DIABHYCAR Study (FAIR)	Primary end point (combined) at 3-6 (median 4) years of followup: ramipril 362/2443 (14.8%) vs placebo 377/2469 (15.3%) RR 0.97 (95% CI 0.85 to 1.11) p=0.66 Also no significant differences on individual components of primary endpoints or on secondary enpoints.	Not reported	1 ramipril and 1 placebo patient developed angioedema; 6.3% ramipril and 4.0% placebo reported non-serious adverse events (cough most frequent); 43.2% ramipril vs 44.4% placebo reported serious adverse events (most frequent inadequate control of diabetes).	14% of ramipril vs 13.5% placebo withdrew 3.3% ramipril vs 0.9% placebo withdrew due to coughing.
MacMahon, 2000 Australia and New Zealand PART2 Trial (FAIR)	CV events NNT 44.8 RR 0.83 (0.54-1.28) All-cause mortality RR 0.64 (0.35-1.18)	Not reported	Not reported	Not reported
Pitt, 2001 US, Canada, Europe QUIET Study (FAIR)	CV events NNT 139 RR 0.88 (0.61-1.29) Too small to assess all-cause mortality.	Not reported	Not reported	"Frequency and reasons for withdrawal in placebo and quinapril were similar. Cough was the only treatment-associated adverse event leading to a significantly higher percentage of withdrawals in the quinapril than placebo group." (3.8% vs 0.2%)

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)
Teo, 2000 Canada SCAT Trial (FAIR)	2 X 2 factorial design (simvastatin and enalapril) Multicenter	Age 21 or older, total serum cholesterol 4.1-6.2 mmol/L, HDL cholesterol <2.2 mmol/L and triglycerides <4 mmol.L and lower than total cholesterol, angiographically detectable coronary atherosclerosis in 3 or more major coronary arter segments, and left ventricular ejection fraction >35%. Patients not enrolled within 6 months of coronary angioplasty or bypass surgery.	Enalapril 5-20 mg

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Run-in/Washout	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Teo, 2000 Canada SCAT Trial (FAIR)	1-month, single-blind, placebo run-in. Criteria for withdrawal after run-in not reported.	2 X 2 factorial design included simvastatin; all patients instructed to follow cholesterol-lowering diet.	Study endpoints were Quantitative coronary angiography measures and prespecified clinical events (death, MI, stroke, hospitalization for angina, revascularization, and cancer). Clinical endpoints were not powered to detect conclusive differences. Followup 4 years

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Teo, 2000 Canada SCAT Trial (FAIR)	Mean age 61 (SD 9) 89% male Ethnicity not reported	History: 54% angina; 70% MI, 11% diabetes, 36% hypertension, 15% current smoker, 67% previous smoker.	>16,500 charts and 4,000 coronary angiograms screened/number eligible not reported: "one third of patients entering run-in were not randomized"/460 enrolled/	Not reported for clinical endpoints.

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author Year Country (Quality Rating)	Results	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals/withdrawals due to adverse events
Teo, 2000 Canada SCAT Trial (FAIR)	CV events NNT 16 RR 0.47 (0.24-0.90) Too small to assess all-cause mortality.	Monitored (serum biochemical monitoring)	No differences in frequency of elevated serum potassium and creatinine levels between groups.	Not reported

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
EUROPA Investigators, 2003; Gomma 2001 Multiple countries in Eastern and Western Europe EUROPA Study (FAIR)	Method not reported	Method not reported	Yes	Yes	Yes	Not reported
HOPE Study Investigators, 2000, 1996 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial (FAIR)	Yes	Method not reported	Yes	Yes	Yes	Not reported

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?
EUROPA Investigators, 2003; Gomma 2001 Multiple countries in Eastern and Western Europe EUROPA Study (FAIR)	Yes	Attrition and adherence yes crossovers and contamination no	No	Yes, able to calculate; endpoints on all but 3 patients (all perindopril)
HOPE Study Investigators, 2000, 1996 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial (FAIR)	Yes	attrition yes/crossovers no/adherence yes/contamination yes (reports # of placebo patients receiving an ACE inhibitor, but % specifically ramipril not reported)	No	Yes

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Post-randomization exclusions?	Quality Rating	Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/ Washout?
EUROPA Investigators, 2003; Gomma 2001 Multiple countries in Eastern and Western Europe EUROPA Study (FAIR)	No	Fair	Number screened not reported/ 13,655 eligible/ 12,216 enrolled	Clinical evidence of heart failure, planned revascularization, hypotension (SBP <110 mm Hg), uncontrolled hypertension (SBP >180 ,, Hg, DBP >100 mm Hg, or both), recent (<1 month) use of ACE inhibitors or angiotensin-receptor blockers, renal insufficency (creatinine >150 mol/L), and serum ppotassium higher than 5.5 mmol/L.	Run-in
HOPE Study Investigators, 2000, 1996 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial (FAIR)	No	Fair	Number screened not reported/ 10,576 eligible/ 9,297 enrolled	Current use of an ACE inhibitor or vitamin E and inability to discontinue these; known hypersensitivity to an ACE inhibitor or vitamin E; ejectio fraction <40%; hemodynamically significant primary valvular or outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, syncopal episodes presumed to be due to uncontrolled life-threating arrhythmias, planned cardiac surgery or angioplasty within 3 months, uncontrolled hypertension, cor pulmonale, heart transplant recipient; signicicant renal disease, any other major noncardiac illness expected to reduce life expectancy or interfere with study participation; simultaneously taking anohter experimental drug, previously randomized by HOPE.	Run-in

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Class-naive patients?	Control group standard of care?	Funding	Relevance
EUROPA Investigators, 2003; Gomma 2001 Multiple countries in Eastern and Western Europe EUROPA Study (FAIR)	No	Yes	Sponsored by Servier: Paris, France. Authors received honoraria, research grants, or both from the study sponsor.	Relevant
HOPE Study Investigators, 2000, 1996 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial (FAIR)	No	Yes	Funded by the Medical Research Council of Canada, Hoechst-Marion Roussel, Astra-Zeneca, King Pharmaceuticals, Natural Source Vitamin E Association andn Negma, and the Heart and Stroke Foundation of Ontario. First author was supported by a Senior Scientist Award of the Medical Research Council of Canada and a Heart and Stroke Foundation of Ontario Research Chair.	Relevant

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Marre et al. 2004 Multiple European countries DIABHYCAR Study (FAIR)	Yes	Method not reported	Yes	Yes	Yes	Not reported
MacMahon, 2000 Australia and New Zealand PART2	Yes	Yes	Yes	Yes	Yes, but method not described	Not reported
Pitt, 2001, Texter, 1993 US, Canada, Europe QUIET Study	Yes	Method not reported	More prior MI in placebo group (52% vs 47%); more patients in quinapril group taking beta blockers (27% vs 35%) and aspirin (74% vs 71%)	Yes	Yes	Not reported

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?
Marre et al. 2004 Multiple European countries DIABHYCAR Study (FAIR)	Yes	Yes	No	Yes, able to calculate (25/4937 not analyzed)
MacMahon, 2000 Australia and New Zealand PART2	Yes, but method not described	Attrition yes/crossovers no/adherence yes/contamination yes (reports # of placebo and ramipril patients an ACE inhibitor, but % specifically ramipril not reported)	No	Yes for vital status
Pitt, 2001, Texter, 1993 US, Canada, Europe QUIET Study	Yes	Attrition yes/crossovers no/adherence no/contamination yes	No (4 lost, group not reported)	Yes

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Post-randomization exclusions?	Quality Rating	Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/ Washout?
Marre et al. 2004 Multiple European countries DIABHYCAR Study (FAIR)	Yes- 25 patients at 20 centers withdrawn due to misconduct by investigator	Fair	25,468 screened/5948 eligible/4937 enrolled	Serum creatinine concentration >150 mmol/l; treatment with insulin, an ACE inhibitor, or an angiotensin II receptor blocker; documented congestive chronic heart failure, MI during the past 3 months, urinary tract infection, and previous intolerance to an ACE inhibitor.	Not reported
MacMahon, 2000 Australia and New Zealand PART2	No	Fair	Number screened not reported/ 744 eligible/ 617 enrolled	Heart failure or any other definite indication for treatment with an ACE inhibitor, a contraindication to treatment with an ACE inhibitor, serious nonvascular disease, DBP >100 mm Hg, SBP >160 mm Hg or <100 mm Hg during the prerandomizaiton run-in period, or were of childbearing potential without adequate contraception.	Run-in
Pitt, 2001, Texter, 1993 US, Canada, Europe QUIET Study	No	Fair	Number screened not reported/ number eligible not reported/ 1,750 enrolled	LDL cholesterol >165 mg/dl, coronary artery bypass graft surgery, SBP <100 mm Hg or >160 mm Hg and/or DBP >100 mm Hg; ejection fractin <40%; MI within 7 days; prior angioplasty within 3 months; and those receiving lipid-lowering medications, ACE inhibitors, or calcium channel blockers.	No

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Class-naive patients?	Control group standard of care?	Funding	Relevance
Marre et al. 2004 Multiple European countries DIABHYCAR Study (FAIR)	No	Yes	Supported by a grant from Aventis (Paris) and by a Programme Hospitalier de Recherche Clinique (French Health Ministry).	Low dose of ramipril (1.25 mg day)
MacMahon, 2000 Australia and New Zealand PART2	No	Yes	Supported by a project grant from Hoeschst AG, the manufacturers of ramipril and by a program grant from the Health Research Council of New Zealand.	Relevant
Pitt, 2001, Texter, 1993 US, Canada, Europe QUIET Study	No	Yes?	Suppported by Parke-Davis Pharmaceutical Research, Ann Arbor, MI.	Relevant

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Teo, 2000, Teo, 1997 Canada SCAT Trial	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?
Teo, 2000, Teo, 1997 Canada SCAT Trial	Yes	adherence yes	unable to determine	unable to determine

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Post-randomization exclusions?	Quality Rating	Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/ Washout?
Teo, 2000, Teo, 1997 Canada SCAT Trial	No	Fair	>16,500 charts and 4,000 coronary angiograms screened/ number eligible not reported ("one third of patients entering run-in were not enrolled")/ 460 enrolled/	Within 6 months of coronary angioplasty or bypass surgery; clear indications for or contraindications to study drugs, clinical instability, imminent need for intervention, other significant cardiac or systemic diseases, potential noncompliance, and inability to give informed consent.	Placebo washout

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Class-naive patients?	Control group standard of care?	Funding	Relevance
Teo, 2000, Teo, 1997 Canada SCAT Trial	No	Yes	Financial and in-kind support from the Medical Research Council of Canada, Merck Frosst Canada & Co, the Alberta Heritage Foundation for Medical Research, University of Alberta Hospitals, and Safeway Canada. The principal investigator has received unrestricted grants from Merck Frosst Canada & Co, as part of the Medical Reserach Council of Canada University-Industry Program. Co-principal investigator is now an employee of Merck Frosst Canada & Co. (was not at the time of the study)	Relevant

Evidence Table 3. Head-to-head trials of ACEIs for recent myocardial infarction

Author, Year Country Quality	Interventions (drug, regimen, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Foy (PRACTICAL trial) 1994 New Zealand Fair	A: Captopril 6.25 mg po q 2 hours x 3 doses, then 25 mg tid B: Enalapril 1.25 mg po q 2 hours x 3 doses, then 5 mg tid C: Placebo 12 months	Patients presenting within 24 hours of chest pain with ST segement elevation, new Q waves, or elevation of creatinine phosphokinase	Captopril vs. enalapril vs. placebo Mean age (years): 64 vs. 63 vs. 64 Female gender (%): 16 vs. 16 vs. 7 Race: Not reported	Prior MI (%): 17 vs. 13 vs. 11 Beta-blocker at entry (%) 25 (p=0.046) vs. 11 vs. 15 Anterior MI (%): 45 vs. 49 vs. 49 Mean peak CK: 1762 vs. 1949 vs. 1979	523 screened 406 eligible 225 enrolled	42 withdrawn Lost to follow-up not clear 167 analyzed
Lau 2002 China Fair	A: Captopril 6.25 mg po x 1, then 12.5 mg x 1 2 hours later, then 25 mg x 1 10-12 hours later, then 25 mg po bid x 1 day, then 50 mg po bid B: Perindopril 2 mg po x 1, then 4 mg po qD x 1, then 8 mg po qD 6 months	Aged 18-85 years presenting within 72 hours of acute MI by ECG, creatine kinase, and symptoms criteria	Captopril vs. perindopril: Mean age (years): 65 vs. 64 Female gender (%): 19 vs. 28 Race: Not reported	Captopril vs. perindopril Anterior MI (%): 47 vs. 46 Killip class: 1.2 vs. 1.4 Peak CK: 2045 vs. 2020 Beta-blocker use prior to entry (%): 6 vs. 13	Not reported Not reported 212 enrolled	None reported withdrawn or lost to follow-up 212 analyzed

Evidence Table 3. Head-to-head trials of ACEIs for recent myocardial infarction

Author, Year Country Quality	Method of Outcome Assessment and Timing of Assessment	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
Foy (PRACTICAL trial) 1994 New Zealand Fair	Radionuclide ventriculography Renin-angiotensin levels Mortality Assessed at baseline, 90 days, 12 months	Captopril vs. enalapril vs. placebo: Mortality (90 days): 9/75 vs. 1/75 (p=0.038) vs. 7/75 Mortality (12 months): 10/75 vs. 2/75 (p=0.022) vs. 12/75	Not reported	Captopril vs. enalapril vs. placebo Withdrawals (overall): 24% vs. 16% vs. 16% Withdrawals (adverse events): Not clear Adverse event requiring dose reduction: 8/75 vs. 4/75 vs. 0/75 Dizziness: 15/75 vs. 14/75 vs. 6/75 Rash: 6/75 vs. 4/75 vs. 0/75 Cough: 6/75 vs. 4/75 vs. 2/75 Loss of taste: 5/75 vs. 1/75 vs. 0/75 GI upset: 2/75 vs. 0/75 vs. 1/75 Headache: 0/75 vs. 1/75 vs. 1/75
Lau 2002 China Fair	Laboratory screning, ECG, blood pressure monitoring Every 12 hours during the first 48 hours, then at 3 and 6 months	Captopril vs. perindopril Mortality (6 months): 13% (13/102) vs. 6% (7/110) (p=0.12) Revascularization (6 months): 21% (21/102) vs. 20% (22/110) (p=0.9)	Not reported	Any adverse events: 17% vs. 13% (NS) Withdrawals (overall): 14% vs. 9% (NS) Hypotension: 3% vs. 2% (p=0.67) Cough: 5% vs. 3% Acute symptomatic hypotension: 7% vs. 2% (p=0.09)

Evidence Table 4. Quality assessment of head-to-head trials of ACEIs for recent myocardial infarction

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Foy (PRACTICAL Trial) 1994 New Zealand	Method not specified	Not described	Significantly more patients on beta-blockers in captopril group	Appears similar	Yes	Method not reported	Method not reported	Not clear
Lau 2002 China	Method not specified	Not described	Significantly higher Killip class (1.4 vs. 1.2, p=0.05) in perindopril group	Appears similar	Yes	Not clear	Not clear	Not clear

Evidence Table 4. Quality assessment of head-to-head trials of ACEIs for recent myocardial infarction

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)	Funding	Control group standard of care?	Length of follow-up
Foy (PRACTICAL Trial) 1994 New Zealand	Not clear	Yes	No	No	**Fair**	Merck and Bristol-Myers, role not specified	Yes	12 months
Lau 2002 China	Yes	Yes	No	No	**Fair**	Not reported	Yes	6 months

Evidence Table 5. Randomized controlled trials of ACEIs for recent myocardial infarction

Study, year	Interventions	Duration of intervention	Number enrolled	All-cause mortality at end of intervention	Overall quality
Head-to-head trials of one ACEI vs. another ACEI					
Foy (PRACTICAL) 1994	A: Captopril B: Enalapril	12 months	225	13% (10/75) 3% (2/75) (p=0.022)	Fair
Lau 2002	A: Captopril B: Perindopril	6 months	212	13% (13/102) 6% (7/110) (p=0.12)	Fair
Trials of Captopril vs. placebo					
Pfeffer (SAVE) 1992	A: Captopril B: Placebo	Mean 42 months	2231	20% (228/1115) 25% (275/1116) (NS)	Good
Kingma (CATS) 1994	A: Captopril B: Placebo	3 months	298	6% (9/149) 4% (6/149) (NS)	Fair
ISIS-4 1995	A: Captopril B: Placebo	4 weeks	58050	7.2% (2088/29028) 7.7% (2231/29022) (p=0.02)	Good
Shen 1996	A: Captopril B: Placebo	21-22 months	822	In-hospital mortality 7% (33/478) 18% (62/344) (p<0.05)	Fair
Kleber (ECCE) 1997	A: Captopril B: Placebo	4 weeks	208	2% (2/104) 3% (3/104) (NS)	Fair
CCS-1 1997	A: Captopril B: Placebo	4 weeks	6749	9.1% (681/7468) 9.7% (730/7494) (NS)	Fair
Trials of other ACEIs vs. placebo					
Swedberg (CONSENSUS II) 1992	A: Enalapril B: Placebo	6 months	6090	10.2% (312/3044) 9.4% (286/3046) (NS)	Good
AIRE 1993	A: Ramipril B: Placebo	6-15 months	2006	17% (170/1004) 23% (222/982) (p=0.002)	Good
Borghi (FAMIS) 1998	A: Fosinopril B: Placebo	3 months	285	8.4% (11/131) 5.2% (7/134) (NS)	Fair
GISSI-3 1994	A: Lisinopril B: Placebo (open)	6 weeks	19394	6.4% (519/9646) 7.2% (693/9672) (p not reported)	Good (not blinded)
Kober (TRACE) 1995	A: Trandolapril B: Placebo	24 months	1749	35% (304/876) 42% (369/873) (p=0.001)	Good

Evidence Table 6. Results of systematic reviews of randomized controlled trials of ACEIs from recent myocardial infarction

Trials included in our evidence tables are in bold.

Study	Intervention	Mortality (odds ratio for ACE-I vs. placebo)	95% confidence interval
Trials of long-term (>6 weeks) ACEI post-myocardial infarction (Domanski 1999, Flather 2000)			
AIRE 1993	Ramipril	0.70	0.56-0.87
CATS 1994	Captopril	1.31	0.57-3.05
CONSENSUS 2 1992	Enalapril	1.10	0.93-1.31
ECCE 1997	Enalapril	0.71	0.14-3.67
EDEN 1997	Enalapril	1.48	0.06-36.56
EDI 1997	Enalapril	2.74	0.11-69.15
Mortarino 1990	Captopril	1.10	0.02-60.30
Nabel 1991	Captopril	0.29	0.01-7.44
Oldroyd 1991	Captopril	1.69	0.54-5.36
PRACTICAL 1994	Enalapril or captopril	0.46	0.20-1.06
SAVE 1992	Captopril	0.79	0.64-0.96
Sharpe 1991	Captopril	1.43	0.27-7.61
SMILE 1995	Zofenopril	0.77	0.52-1.12
Sogaard 1994	Captopril	1.00	0.10-10.20
TRACE 1995	Trandolapril	0.73	0.60-0.88
Trials of short-term (<6 weeks) ACEI post-myocardial infarction (Collaborative group,1998)			
ISIS-4 1995	Captopril	0.93	0.87-0.99
CCS-1 1997	Captopril	0.94	Not reported
CONSENSUS 2 1992	Enalapril	1.10	0.93-1.29
GISSI-3 1994	Lisinopril	0.88	0.79-0.99

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Interventions (drug, regimen, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Anonymous (AIRE study investigators) 1993 International (GOOD)	A: Ramipril 2.5 mg bid started on day 3-10 after MI for 2 days, then 5 mg bid if tolerated B: Placebo Minimum of 6 months, average 15 months	Over 18 years, admitted to hospital with definite acute MI and clinical evidence of heart failure after MI.	Ramipril vs. placebo Mean age (years): 65 vs. 65 Female gender (%): 27 vs. 26 Race: Not reported	Previous MI (%): 29 vs. 27 Diabetes (%): 12 vs. 12 Anterior MI (%): 62 vs. 59 Beta-blocker at entry (%): 24 vs. 21	52019 screened Number eligible about 4000 2006 enrolled
Anonymous (CCS-1 trial) 1997 China (FAIR)	A: Captopril 6.25 mg po initially, then 12.5 mg po 2 hours later, then 12.5 mg po tid B: Placebo 4 weeks	Patients within 36 hours of the onset of symptoms of suspected acute MI (with or without ST elevation)	Captopril vs. placebo Mean age (years): 61 vs. 61 Female gender (%): 26 vs. 26 Race: Not reported, presumed Asian	Previous MI (%): 12 vs. 12 Diabetes (%): 9 vs. 9 Killip class III (%): 9 vs. 9 Killip class IV (%); 3.3 vs. 3.5	Numbers screened and eligible not reported 14962 enrolled

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Method of Outcome Assessment and Timing of Assessment	Outcomes	Method of adverse effects assessment
Anonymous (AIRE study investigators) 1993 International (GOOD)	Mortality, clinical evaluation, renal function Clinical evaluation at 4 and 12 weeks after randomization, then every 12 weeks until end of study	Ramipril vs. placebo Mortality (overall): 17% (170/1004) vs. 23% (222/982) (RRR=27%, p=0.002) First validated events: Mortality: 9% (94/1004) vs. 12% (118/982) Severe or resistant heart failure: 10% (103/1004) vs. 14% (133/982) Reinfarction: 7% (68/1004) vs. 7% (71/982) Stroke: 2% (21/1004) vs. 2% (15/982) Any event: 28% (286/1004) vs. 34% (337/982) (p=0.008)	Serious adverse events pre-defined Adverse events assessed by coordinating center or by independent steering committee
Anonymous (CCS-1 trial) 1997 China (FAIR)	Mortality, clinical assessment, ECG Evaluated at baseline, 4 weeks	Captopril vs. placebo Mortality (4 weeks): 9.1% (681/7468) vs. 9.7% (730/7494) (NS) Heart failure: 17% (1272/7468) vs. 19% (1398/7494) (p=0.01) Death or heart failure: 21% vs. 23% (p=0.02) Reinfarction: 5% (362/7468) vs. 5% (350/7494) (NS)	Not specified

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Adverse Effects Reported	Comments
Anonymous (AIRE study investigators) 1993 International (GOOD)	Ramipril vs. placebo Withdrawals (overall): 35% (352/1004) vs. 32% (318/982) Withdrawals (adverse events): 13% (126/1004) vs. 7% (68/982) Serious adverse events (including endpoints of the trial): 58% (581/1004) vs. 64% (625/982) Syncope: 2.4% (24/1004) vs. 1.7% (17/982) Hypotension: 4% (42/1004) vs. 2% (23/982) Renal failure: 1.5% (15/1004) vs. 1.2% (12/982) Angina: 18% (181/1004) vs. 17% (171/982)	
Anonymous (CCS-1 trial) 1997 China (FAIR)	Captopril vs. placebo Withdrawals: Not reported Profound hypotension: 8.0% (594/7468) vs. 4.7% (350/7494) (p=0.001) Cough: 5.0% vs. 4.2% (p=0.02) Agranulocytosis: 0.3% vs. 0.1% (p=0.02)	2 year follow-up: Mortality (2 years): 11.9% (404/3391) vs. 13.8% (463/3358) (p=0.03) Reinfarction (2 years): 5.6% vs. 6.0% (p=0.50) Total cardiovascular events (2 years): 33% vs. 34% (p=0.25) (Liu L. Chin Med J 2001;114:115-118)

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Interventions (drug, regimen, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Anonymous (GISSI-3) 1994/1996 Italy	A: Lisinopril 5 mg initially, 5 mg after 24 hours, 10 mg after 48 hours, then 10 mg po qD B: Placebo (open) 6 weeks	Chest pain with ST segment changes consistent with acute ischemia, admitted to cardiac care unit within 24 hours of onset of symptoms, and no clear contraindications to interventions	Lisinopril vs. placebo Age >70 (%): 27 vs. 27 Female gender (%): 22 vs. 22 Race: Not reported	Previous MI (%): 14 vs. 14 Anterior MI (%): 27 vs. 28 Diabetes (%): 16 vs. 16 IV beta-blockers given (%): 30 vs. 31	43047 screened Number eligible not clear 19394 enrolled
Anonymous (ISIS-4 collaborative group) 1995 International (GOOD)	A: Captopril 6.25 mg po initially, then 12.5 mg po 2 hours later, then 25 mg po 12 hours later, then 50 mg po bid B: Placebo 28 days	Within 24 hours of onset of symptoms for acute MI with no clear indications for, or contraindications to ACEI, nitrates, or magnesium	Captopril vs. placebo Age >70 (%): 15 vs. 15 Female gender (%): 11 vs. 11 Race: Not reported	Previous MI (%): 9 vs. 11 Anterior ST elevation (%): 8.5 vs. 9.8 IV beta-blocker in hospital (%): 6 vs. 6	Numbers screened and eligible not reported 58050 enrolled

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Method of Outcome Assessment and Timing of Assessment	Outcomes	Method of adverse effects assessment
Anonymous (GISSI-3) 1994/1996 Italy	Echocardiography, clinical evaluation, EKG Assessed weekly	Lisinopril vs. placebo Mortality (6 weeks): 6.4% (619/9646) vs. 7.2% (693/9672) Heart failure: 3.8% vs. 3.7% Ejection fraction <35%: 4.7% vs. 5.5% Combined primary endpoints: 15.5% vs. 16.8% (p=0.04)	Clinical exam, otherwise not clear
Anonymous (ISIS-4 collaborative group) 1995 International (GOOD)	Discharge forms and government records for mortality Evaluated at baseline, discharge, and at end of study	Captopril vs. placebo Mortality (5 weeks): 7.2% (2088/29028) vs. 7.7% (2231/29022) (p=0.02) Mortality (12 months): 12.0% vs. 12.5% (p<0.01) Angina: 16% vs. 16% CABG or PTCA: 4.6% vs. 4.5% Reinfarction: 4.1% vs. 3.9%	Discharge form evaluated to assess in-hospital adverse events

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Adverse Effects Reported	Comments
Anonymous (GISSI-3) 1994/1996 Italy	Lisinopril vs. placebo: Withdrawals: Not reported Persistent hypotension: 9% vs. 4% (p<0.05) Renal dysfunction: 2.4% vs. 1.1% (p<0.05)	Mortality benefits maintained at 6 month follow-up: 9.1% (882/9646) vs. 9.6% (928/9672) Heart failure: 5.4% vs. 5.8% Ejection fraction <35%): 3.3% vs. 3.7% Combined primary endpoints: 18.1% vs. 19.3% (p=0.03) Reinfarction (6 months): 4.7% vs. 4.6% (NS) Angina: 28% vs. 27% (NS) CABG: 4.8% vs. 4.3% (NS) PTCA: 4.0% vs. 3.8% (NS) (Anonymous. J Am Coll Cardiol 1996;27:337-344)
Anonymous (ISIS-4 collaborative group) 1995 International (GOOD)	Captopril vs. placebo Withdrawals: Not reported Profound hypotension requiring termination of treatment: 10% vs. 5% (p<0.001) Cardiogenic shock: 4.6% vs. 4.1% (p<0.01) Heart block: 17% vs. 17% Dizziness: 0.5% vs. 0.4% (p<0.01) Renal dysfunction: 1.1% vs. 0.6% (p<0.0001)	Subgroup analysis of diabetic patients (n=2790) found lisinopril associated with decreased 6-week mortality (8.7%) vs. placebo (12.4%) (p<0.05); better (p<0.025) than in nondiabetics (Zuanetti G. Circulation 1997;96:4239-4245). Subgroup analysis of patients with hypertension (n=7362) found no significant benefit for combined end point of mortality or left ventricular dysfunction at 6 weeks (18.0% vs. 18.3%), but did find a significant benefit in normotensives (n=10661) (13.7% vs. 15.8%) (Avanzini F. Am Heart J 2002;144:1018-1025). Benefits of early treatment with lisinopril maintained after 6 months: mortality or severe ventricular dysfunction 18.1% vs. 19.3% (p=0.03) (Anonymous J Am Coll Cariol 1996;27:337-344).

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Interventions (drug, regimen, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Borghi (FAMIS trial) 1998 Italy (FAIR)	A: Fosinopril 5 mg po qD, titrated to 20 mg po qD B: Placebo 3 months (followed up for 2 years)	18-75 years, presented within 9 hours of onset of typical ischemic chest pain associated with ECG changes of definite anterior MI and eligible for thrombolytic treatment	Fosinopril vs. placebo Mean age (years): 60 vs. 60 Female gender (%): 22 vs. 13 Race: Not reported	Prevous anterior MI (%): 17% vs. 19% Diabetes (%): 18% vs. 12% Beta-blocker at randomization (%): 7% vs. 10% Killip class II or III (%): 22% vs. 18%	Number screened and eligible not reported 285 enrolled
Kingma (CATS trial) 1994 Netherlands (FAIR)	A: Captopril 6.25 mg po after streptokinase infused, then titrated to target dose of 25 mg po tid B: Placebo 3 months	Anterior MI, presenting within 6 hours of onset of symptoms, treated with thrombolytic therapy	Captopril vs. placebo Mean age (years): 59 vs. 60 Female gender (%): 30 vs. 20 Race: Not reported	Previous ischemic heart disease (%): 9 vs. 8 Diabetes (%): 9 vs. 9 Killip class I (%): 76 vs. 75 Beta-blocker at randomization (%): 14 vs. 11	Numbers screened and eligible not reported 298 enrolled

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Method of Outcome Assessment and Timing of Assessment	Outcomes	Method of adverse effects assessment
Borghi (FAMIS trial) 1998 Italy (FAIR)	Echocardiography, clinical examination Baseline, at discharge, at 3 onths, and at end of study	Fosinopril vs. placebo Mortality (3 months): 8.4% (11/131) vs. 5.2% (7/134) (NS) Heart failure (3 months): 20% vs. 24% (NS) Mortality or heart failure (3 months): 28% vs. 29% (NS) Ventricular arrhythmia (3 months): 0.8% vs. 6.0% (p=0.02)	Not specified
Kingma (CATS trial) 1994 Netherlands (FAIR)	Echocardiography, longterm ambulatory ECG, lab evaluation, radionuclide ejection fraction, clinical exam Baseline, , pre-discharge, and 3 months	Captopril vs. placebo Mortality: 6% (9/149) vs. 4% (6/149) (NS) Heart failure: 19% (28/149) vs. 28% (42/149) (p=0.05) Heart failure requiring hospitalization: 1% (2/149) vs. 5% (7/149) (NS) PTCA or CABG: 22% vs. 23% (NS) Reinfarction: 7% (10/149) vs. 3% (4/139) (NS)	Not specified

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Adverse Effects Reported	Comments
Borghi (FAMIS trial) 1998 Italy (FAIR)	Fosinopril vs. placebo Withdrawals: Not reported Hypotension: 29% vs. 17% (p=0.004) Persistent hypotension requiring treatment or withdrawal of medication: 10% vs. 10% (NS) Cough: 6% vs. 5% Rash: 0% vs. 2% Rise in creatinine: 8% vs. 6% (NS) Hyperkalemia: 5% vs. 4% (NS)	Open-label study after first 3 months; results also reported in Borghi 1997. 2 year follow-up found mortality 14.5% (captopril) vs. 14.1% (placebo) (NS), heart failure 30% vs. 37% (NS), mortality or heartfailure 45% vs. 52% (NS), mortality or NYHA class III or IV heart failure 18% vs. 27% (p=0.04), angina 18% vs. 16% (NS), reinfarction 7.7% vs. 6.7% (NS), PTCA 7.7% vs. 4.5% (NS), and CABGH 3.8% vs. 3.7% (NS)
Kingma (CATS trial) 1994 Netherlands (FAIR)	Captopril vs. placebo Withdrawals: Not reported Acute hypotension: 21% (31/149) vs. 12% (18/149) Hypotension (3 months): 27% vs. 18% (NS)	12 month follow-up study (van den Heuvel, A. F. M. J Am Coll Cardiol 1997;30:400-5) (n=244) Ischemia related events by 12 months (PTCA, CABG, MI, angina, death): 34% (38/112) vs. 42% (56/132) (NS) Death: 2% (2/112) vs. 2% (3/132) Reinfarction: 2% (2/112) vs. 2% (2/132) Ischemia related events from 3-12 months: 18% (20/112) vs. 32% (42/132) (p=0.018) 12 month follow-up study (van Gilst, W. H. J Am Coll Cardiol 1996;28:114-21) (n=298) Mortality: 9% (13/149) vs. 7% (10/149) Heart failure: 26% (39/149) vs. 36% (53/149) (p<0.03) Reinfarction: 10% (15/149) vs. 4% (6/149) CABG: 8% (12/149) vs. 7% (11/149) PTCA: 23% (34/149) vs. 28% (42/149) Any clinical event: 58% (86/149) vs. 62% (92/149) 12 month follow-up study (Hillege, H.L. Eur Ht Jl 2003;24:412-20) (n=298) Mean decline in GFR (ml/min): 0.5 vs. 5.5 (p<0.05)

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Interventions (drug, regimen, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Kleber (ECCE trial) 1997 Germany (FAIR)	A: Captopril titrated to mean dose of 66 mg/day at end of 4 weeks B: Placebo 4 weeks	Acute MI, enrolled within 24-72 hours of onset of chest pain	Captopril vs. placebo Mean age (years): 59 vs. 64 Female gender: 17% vs. 22% Race: Not reported	Previous MI (%): 11% vs. 8% Diabetes: Not reported Anterior MI: 35% vs. 49% (p=0.048) Beta-blocker on admission (%): 11% vs. 14%	Numbers screened and eligible not reported 208 enrolled
Kober (TRACE trial) 1995 Europe (GOOD)	A: Trandolapril 1 mg po qD started 3-7 days after MI, then 2 mg qD after 2 days, then 4 mg qD after 4 weeks B: Placebo 24 months	Over 18 years, hospitalized with myocardial infarction by clinical symptoms or typical ECG changes, accompanied by increase in cardiac enzymes, evaluated between day 2 and 6 after onset of symptoms, and ejection fraction less than 35%	Trandolapril vs. placebo Mean age (years): 68 vs. 67 Female gender (%): 28 vs. 29 Race: Not reported	Prevoius MI (%): 37 vs. 34 Diabetes (%): 13 vs. 14 Anterior Q wave (%): 47 vs. 47 Kilip class >=2 (%): 21 vs. 21 Beta-blocker (%): 17 vs. 15	7001 myocardial infarctions in 6676 patients screened 2606 eligible 1749 enrolled

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Method of Outcome Assessment and Timing of Assessment	Outcomes	Method of adverse effects assessment
Kleber (ECCE trial) 1997 Germany (FAIR)	Exercise testing, oxygen uptake testing, mortality Baseline, 4 weeks, 3 months	Captopril vs. placebo Death, heart failure requiring ACEI therapy, or VO2max<=10 mL/kg/min (4 weeks): 7% (7/104) vs. 17% (18/104) Death: 2% (2/104) vs. 3% (3/104)	Not specified except that hypotension was closely monitored while in hospital
Kober (TRACE trial) 1995 Europe (GOOD)	Mortality end-point committee, reinfarction end-point committee Baseline, 3 months, 6 months, 1 year, 2 years	Trandolapril vs. placebo Mortality (2 years): 34.7% (304/876) vs. 42.3% (369/873) (p=0.001) Progression to severe heart failure: 14% (125/876) vs. 20% (171/873) (p=0.003) Reinfarction: 11% (99/876) vs. 13% (113/873) (p=0.29)	Not specified

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Adverse Effects Reported	Comments
Kleber (ECCE trial) 1997 Germany (FAIR)	Captopril vs. placebo Withdrawal (overall): 4% vs. 12% Withdrawal (adverse events): Not reported First dose hypotension: 37% vs. 18% (p<0.05) Adverse events possibly, likely, or definitely related to therapy: 36% vs. 30% 'Severe' adverse events: 17% vs. 17% Diastolic blood pressure <60: 22% vs. 12%	
Kober (TRACE trial) 1995 Europe (GOOD)	Trandolapril vs. placebo Withdrawal (overall): 37% (328/876) vs. 36% (310/873) Withdrawal (adverse events): Not clear Angina: NS Chest pain: NS Pneumonia: 10% vs. 15% (p=0.001) Cough: 34% vs. 21% (p<0.001) Hypotension: 31% vs. 22% (p<0.001) Renal dysfunction: 14% vs. 11% (p=0.06) Hyperkalemia: 5% vs. 3% (p=0.01)	Long-term follow-up (minimum 6 years) found increased median lifetime on trandolapril 15.3 months (95% confidence interval 7 to 51); Torp-Pedersen, C.T. Lancet 1999; 354: 9-12. In diabetics (n=347) relative risk of death in group on trandolapril 0.64 (95% CI 0.45 to 0.91) compared to placebo, versus 0.82 (0.69 to 0.97) nondiabetics. Trandolapril reduced the risk of progression to severe heart failure in diabetics (RR 0.38 [0.21 to 0.67]) but not in nondiabetics; Gustafsson I. J Am Coll Cardiol 1999; 34: 83-9. Lower proportion of patients (44%) received thrombolytics than in placebo-controlled trials of other ACEIs.

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Interventions (drug, regimen, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Pfeffer (SAVE trial) 1992 United States (GOOD)	A: Captopril 12.5 mg po tid titrated to 50 mg po tid B: Placebo Mean 42 months	21-80 years, survived 3 days after MI, left ventricular ejection fraction <40%	Captopril vs. placebo Mean age (years): 59 vs. 59 Female gender (%): 17 vs. 18 Race: Not reported	Previous MI (%): 36 vs. 35 Diabetes (%): 21 vs. 23 Killip class I (%): 60 vs. 59 Anterolateral Q wave (%): 56 vs. 54 Beta-blockers within 24 hours of randomization (%): 35 vs. 36	Numbers screened and eligible not reported 2231 enrolled
Shen 1996 China (FAIR)	A: Captopril 6.25 mg initially, then titrated to 12.5-25 mg tid B: Placebo 21-22 months	Presentation within 72 hours of onset of symptoms and no cardiogenic shock	Captopril vs. placebo Mean age (years): 64 vs. 63 Female gender (%): 23 vs. 26 Race: Not performed, presumed Asian	Captopril vs. placebo Previous MI (%): Not reported Diabetes (%): 10% vs. 13% Anterior MI (%): 55% vs. 51% Beta-blocker (%): 51% vs. 70%	Number screened and eligible not reported 822 enrolled

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Method of Outcome Assessment and Timing of Assessment	Outcomes	Method of adverse effects assessment
Pfeffer (SAVE trial) 1992 United States (GOOD)	Mortality, clinical evaluation, renal function Evaluated at baseline, every 2 weeks after randomization, every 3 months during year 1, and every 4 months after year 1	Captopril vs. placebo Mortality: 20% (228/1115) vs. 25% (275/1116) (p=0.02) Revascularization: 14% (154/1115) vs. 17% (195/1116 (p=0.10) Hospitalization for unstable angina: 12% (135/1115) vs. 12% (133/1116) (p=0.930) Clinical MI, revascularization, or hospitalization for unstable angina: 29% (327/1115) vs. 33% (363/1116) (p=0.47) Heart failure requiring open-label ACEI: 11% vs. 16% (p=0.001) Heart failure requiring hospitalization: 14% vs. 17% (p=0.019) Mortality or heart failure or non-fatal MI: 32% vs. 40% (p<0.01)	Not specified
Shen 1996 China (FAIR)	Clinical evaluation Assessed at baseline and every 1-3 months	Captopril vs. placebo Mortality (in-hospital): 7% (33/478) vs. 18% (62/344) (p<0.05) Mortality (21-22 months): Rates not reported, survival curves significantly better in captopril group Heart failure: 5.5% (21/383) vs. 10.9% (31/284) (p not reported)	Not reported

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Adverse Effects Reported	Comments
Pfeffer (SAVE trial) 1992 United States (GOOD)	Captopril vs. placebo Withdrawal (overall): Not reported Withdrawal (adverse events): 6% (68/1115) vs. 3% (39/1116) Significantly more common in captopril arm: Dizziness: 5% Alteration in taste: 2% Cough: 6% Diarrhea: 2%	Additional results published in Rutherford 1994
Shen 1996 China (FAIR)	Not reported	

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Interventions (drug, regimen, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Swedberg (CONSENSUS II trial) 1992 Scandinavia (GOOD)	A: Enalapril at 1 mg IV over 2 hours, then enalapril 2.5 mg po bid starting 6 hours after IV dose, titrated to 20 mg po QD B: Placebo 6 months	Presentation within 24 hours of the onset of chest pain due to acute myocardial infarction with typical EKG changes or elevated cardiac enzymes	Enalapril vs. placebo Mean age (years): 66 vs. 66 Female gender (%): 27 vs. 26 Race: Not reported	Enalapril vs. placebo Previous MI (%): 23 vs. 24 Diabetes (%): 12 vs. 11 Anterior MI (%): 42 vs. 41 Beta-blockers before randomization (%): 66 vs. 67	10387 screened Number eligible not clear 6090 enrolled

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Method of Outcome Assessment and Timing of Assessment	Outcomes	Method of adverse effects assessment
Swedberg (CONSENSUS II trial) 1992 Scandinavia (GOOD)	Clinical assessment, end-point committee, independent safety committee Baseline, 1 month and 6 months	Enalapril vs. placebo Mortality: 10.2% (312/3044) vs. 9.4% (286/3046) (p=0.26) >=1 hospitalization for heart failure: 4% (130/3044) vs. 6% (174/3046) (NS) Change of therapy because of heart failure: 27% vs. 30% (p<0.006) Reinfarction: 9% (271/3044) vs. 9% (268/3046) (NS)	Independent safety committee, otherwise not clear

Evidence Table 7. Placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country (QUALITY)	Adverse Effects Reported	Comments
Swedberg (CONSENSUS II trial) 1992 Scandinavia (GOOD)	Enalapril vs. placebo Withdrawal (overall): 18% (538/3044) vs. 12% (374/3046) (p<0.001) Withdrawal (adverse events): 9.7% (296/3044) vs. 4.5% (138/3046) (p<0.001) Hypotension below 90/50 initially: 12% vs. 3% (p<0.001) Any adverse event: 74% vs. 70% (p<0.001) Angina: 14% vs. 15% (NS) Hypotension (at any time): 25% vs. 10% (p<0.001) Heart failure: 25% vs. 28% (p=0.012) Increased creatinine: 2.4% vs. 1.0% (p<0.001) Diarrhea: 1.5% vs. 0% (p=0.024) Cough: 6.8% vs. 3.1% (p<0.001)	Trial stopped early because of high likelihood that the null hypothesis would apply. Quality of life (Nottingham Health Profile, Physical symptoms distress Index, Work Performance Scale, and the Life Satisfaction Index) on enalapril after acute MI not significantly different than placebo in substudy of 132 patients 4-6 months after MI (Ekebert, O. Eur Ht Journal 1994; 15: 1135-1139).

Evidence Table 8. Quality assessment of placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population	How many recruited	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Anonymous (AIRE study investigators) 1993 International	Randomization code, numbers allocated in blocks of ten	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes
Anonymous (CCS-1 trial) 1997 China	Computer generated	Not specified	Yes	Yes	14962 screened	Yes	Not clear	Not clear	Not clear
Anonymous (GISSI-3) 1996 Italy	Computer generated	Not specified	Yes	Yes	43047 screened	Yes	No	No	No
Anonymous (ISIS-4 collaborative group) 1995 International	Computer generated	Not specified	Yes	Yes	Not reported	Yes	Yes	Yes	Yes
Borghi (FAMIS trial) 1997 Italy	Not reported	Not specified	No, fosinopril group had more severe heart failure	Yes	Not reported	Yes	No, after 3 months	No, after 3 months	No, open-label after 3 months
Kingma (CATS trial) 1994 Netherlands	Not reported	Not specified	Yes	Yes	Not reported	Yes	Yes	Yes	Yes
Kleber (ECCE trial) 1997 Germany	Blocks of six, otherwise not reported	Not specified	Yes	Yes	Not reported	Yes	Not clear	Yes	Not clear

Evidence Table 8. Quality assessment of placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)	Funding	Control group standard of care	Length of follow-up
Anonymous (AIRE study investigators) 1993 International	Yes	Yes	Yes	No	Good	Hoechst, not clear if data held by funder	Yes	6-15 months
Anonymous (CCS-1 trial) 1997 China	Yes	Yes	No	Not clear	Fair	None reported	Yes	2 years
Anonymous (GISSI-3) 1996 Italy	Yes	Yes	Yes	No	Good (not blinded)	Zeneca pharmaceutical	Yes	6 weeks
Anonymous (ISIS-4 collaborative group) 1995 International	Yes	Yes	Yes	No	Good	None reported	Yes	12 months
Borghi (FAMIS trial) 1997 Italy	Yes	Not clear	No	Not clear	Fair	Bristol-Myers	Yes	2 years
Kingma (CATS trial) 1994 Netherlands	Yes	Yes	Yes	No	Fair	Bristol-Myers	Yes	3 months
Kleber (ECCE trial) 1997 Germany	Yes	Yes	Yes	No	Fair	Schwarz Pharma	Yes	4 weeks

Evidence Table 8. Quality assessment of placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population	How many recruited	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Kober (TRACE trial) 1995 Europe	Computer generated	Not specified	Yes	Yes	6676 screened	Yes	Yes	Yes	Yes
Pfeffer (SAVE trial) 1992 United States	Computer generated	Not specified	Yes	Yes	Not reported	Yes	Not clear	Not clear	Not clear
Shen (Shanghai Second Prevention of AMI trial)	Not reported	Not specified	No, captopril had more patients on beta-blockers	Yes	Not reported	Yes	Not clear	Not clear	Not clear
Swedberg (CONSENSUS II trial) 1992 Scandinavia	Stratified in blocks of 2 to 10	Not specified	Yes	Yes	10387 screened	Yes	Yes	Not clear	Not clear

Evidence Table 8. Quality assessment of placebo-controlled trials of ACEI for recent myocardial infarction

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)	Funding	Control group standard of care	Length of follow-up
Kober (TRACE trial) 1995 Europe	Yes	Yes	Yes	No	Good	Roussel-Uclaf and Knoll	Yes	24-50 months
Pfeffer (SAVE trial) 1992 United States	Yes	Yes	Yes	No	Good	Bristol-Myers, did not hold data	Yes	42 months
Shen (Shanghai Second Prevention of AMI trial)	Not clear	Not clear	Yes	High overall loss to follow-up (19% overall)	Fair	None reported	Yes	21-22 months
Swedberg (CONSENSUS II trial) 1992 Scandinavia	Yes	Yes	Yes	No	Good	Merrck Sharp and Dohme Research Laboratories	Yes	6 months planned, trial stopped early

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Acanfora 1997 Italy Multicenter (Fair)	65 Quinapril 66 Captopril	A: Quinapril 10 mg once daily for 4 weeks, then titrated to 20 mg once daily on physician judgment if no major adverse reactions and if BP not < 110/70. B: Captopril 12.5 mg BID for 4 weeks, then titrated to 25 mg BID on physician judgment if no major adverse reactons and if BP not <110/70. 12 weeks	
Bach 1992 Germany, Italy Multicenter (Poor)	148 Lisinopril 139 Captopril	A: Lisinopril 5 mg once daily, increased to 10 mg at 2 weeks and 20 mg at 4 weeks if no hypotension and if need for additional therapeutic effect. Dose reduced if hypotension or other adverse event occurred. B: Captopril 12.5 mg BID, increased to 25 mg BID at 2 weeks and 50 mg BID at 4 weeks if no hypotension and if need for additional therapeutic effect. Dose reduced if hypotension or other adverse event occurred. 12 weeks	Over age 21 with HF Class II and III, capable of exercise protocol 4-12 minutes, symptomatic on stable doses of digitalis or diuretics or both.

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Allowed other medications/ interventions	Age Gender Ethnicity	Baseline NYHA Class	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
Acanfora 1997 Italy Multicenter (Fair)	NR.	Quinapril vs Captopril: Mean Age 61.5 (sd 8.6) vs 61.3 (sd 10) 77% vs 75% male Ethnicity NR	Quinapril vs Captopril: Class I: 0% vs 1.5% Class II: 65% vs 69% Class III: 35% vs 29%	# screened NR # eligible NR 131 enrolled	2 withdrew 1 died 131 analyzed
Bach 1992 Germany, Italy Multicenter (Poor)	Placebo baseline of 10-14 days during which time digoxin and/or diuretic doses optimized, all other vasodilator and ACE Inhibitors withdrawn.	Lisinopril vs Captopril: Mean age 59 (29-83) vs 59 (33-82) 79% vs 78% male Ethnicity NR	Baseline NYHA Class NR Etiology of heart failure, Lisinopril vs Captopril: Ischemic heart disease: 52% vs 49% Cardiomyopathy: 35% vs 41% Valvular heart disease: 14% vs 8% Hypertension: 22% vs 18% Other: 9% vs 5%	# screened NR 315 eligible 287 enrolled	38 withdrew 252 analyzed

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Method of Outcome Assessment and Timing of Assessment	Results	Adverse Effects Reported
Acanfora 1997 Italy Multicenter (Fair)	Clinical exam during 2-week run-in and every 2 weeks during treatment. BP, clinical signs and symptoms recorded and patients classified according to NYHA class. Exercise test at tend of run-in and after 4 and 12 weeks of treatment. Self-reports of adverse effects.	Quinapril vs Captopril NYHA Class at Week 12: Class I 8% vs 3% (p=NS) Class II 86% vs 75% (p=NS) Class III 6% vs 22% (p<0.05) Exercise duration (minutes) at week 12: 7.8 ± 1.9 vs 7.1 ± 2.3 (p=NS) Stopped exercise test due to fatigue: 32% vs 26% (p NR)	Quinapril: 1 patient died suddenly, 0 patients reported side effects. Captopril: 2 dropped out due to persistent dry cough, 3 patients moderate dry cough, 1 taste blindness, 1 unstable angina.
Bach 1992 Germany, Italy Multicenter (Poor)	Physical exam at entry, abbreviated symptom review and physical exam at randomization and at end (12 weeks). Exercise testing with bicycle ergometer, 2 tests during run-in, at 6 and 12 weeks of treatment. NYHA class assessment done by same observer at end of run-in and at end.	Lisinopril vs Captopril NYHA Class: 35% vs 40% showed improvement 63% vs 58% no change 1.6% vs 1.6% deteriorated (p-values NR) Exercise capacity: after 12 weeks, exercise duration increased by both. Increase slightly greater for Lisinopril, but NS (5 seconds, p=0.68) Symptom review and physical exam: regarding % of patients improving, effect similar for both.	Lisinopril vs Captopril Adverse events reported: 16% vs 15% (p= NS) Withdrawals due to adverse events (including death): 6% vs 5% (p=NS) 5 deaths vs 2 deaths Cause of death: pulmonary edema, ventricular fibrillation, sudden death (n=2), accident vs cardiac failure after MI, pulmonary edema Adverse events not leading to withdrawal: 10% vs 11%

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Beynon 1997 Open Single center (Poor)	31 Captopril 30 Quinapril	A: Captopril titrated every 2 weeks to 16-week maintenance phase: 6.25 mg BID, 12.5 mg BID, 25 mg BID, 50 mg BID. B: Quinapril titrated every 2 weeks to 16-week maintenance phase: 2.5 mg once daily, 5 mg once daily, 10 mg once daily, 20 mg once daily. 16 weeks after 2 to 8 weeks titration.	Over age 64, weight >45 kg, NYHA Class II or III with etiology of ischemic heart disease, ambulatory, stable, on maintenance diuretics not exceeding 80 mg frusemide per day or equivalent.
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	182 Cilazapril 87 Captopril	A: Cilazapril 0.5 mg once daily for 1 week, then increased to 1 mg once daily. If inadequate response after 4 weeks, increased to 2.5 mg once daily. B: Captopril 6.25 mg three times daily, then increased to 25 mg three times daily. If inadequate response after 4 weeks, increased to 50 mg three times daily.	NYHA Class II, III, or IV, clinically stable on digoxin and/or diuretics, over age 18.

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Allowed other medications/ interventions	Age Gender Ethnicity	Baseline NYHA Class	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
Beynon 1997 Open Single center (Poor)	NR.	NR. States no statistically significant differences between treatment groups at baseline regarding age, sex, race.	(Reported for only 36 evaluable patients): Captopril vs Quinapril: Class II: 63% vs 75% Class III: 38% vs 25%	# screened NR # eligible NR 61 enrolled	23 withdrew 2 lost to followup 36 analyzed
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	Digoxin and/or diuretics.	Mean age 63 years (range 21-87) 64% male Ethnicity not reported (states no differences between groups)	Class II: 62% Class III: 36% Class IV: 1% (states no difference between groups)	# screened NR # eligible NR 443 enrolled	76 incomplete data 367 analyzed

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Method of Outcome Assessment and Timing of Assessment	Results	Adverse Effects Reported
Beynon 1997 Open Single center (Poor)	6-minute walking measures and functional life-scale assessment	Captopril vs Quinapril NYHA Class 23% deteriorated, 68% no change, 10% improved vs 0% deteriorated, 83% no change, 17% improved (p=0.02) Six-minute walking test, mean improvement in distance walked 83.1 meters vs 72.2 meters (p=0.84) Functional life scale mean changes NS (p=0.86) cardiothoracic ratio 1.2% decrease vs 0.3% decrease (NS clinically or statistically)	Captopril vs Quinapril: Number of adverse events 71 (18 considered treatment-related) vs 76 (28 considered treatment-related)
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	Quality of life questionnaires: sickness impact profile (SIP), profile of mood states(POMS), other questions to assess dyspnea and ascertain the impact of ill health on leisure and regular activities. Health Status Index (HSI) calculated from questionnaire responses. Assessed at entry, after 12 weeks, and 24 weeks, or at the final visit whenever possible. Self-administered except for Mahler index of dyspnea.	Cilazapril vs Captopril Sickness Impact Score mean change from baseline at 12 weeks (scale 0-48): -2.29 vs -2.93 (NS) Profiile of Mood States mean change from baseline at 12 weeks (scale 0-149): -5.46 vs -7.34 (NS) Health Status Index mean change from baseline at 12 weeks (+ = improvement): +0.04 vs +0.04 (NS)	Not reported

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	221 Cilazapril 108 Captopril	A: Cilazapril 0.5 mg once daily for one week, then 1 mg up to week 4; if no improvement increased to 2.5 mg once daily B: Captopril 6.25 mg TID for one week, then 25 mg TID up to week 4; if no improvement increased to 50 mg TID. 24 weeks	HF NYHA classes II-IV, 18 years or older, chronic HF (onset >3 months), and clinically stable on digitalis and/or diuretics.

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Allowed other medications/ interventions	Age Gender Ethnicity	Baseline NYHA Class	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	Digitalis.	Cilazapril vs Captopril: mean age 63.0 (range 32-87, SD 10.1) vs 62.2 (range 21-85, SD 11.6) 67% vs 63% male 100% vs 99% white	Cilazapril vs Captopril: Class II: 62% vs 56% Class III: 36% vs 42% Class IV: 1% vs 2% Missing: 0.5% vs 0	# screened NR # eligible NR 443 analyzed	22% cilazapril and 25% captopril withdrew lost to followup not reported # analyzed not clear

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Method of Outcome Assessment and Timing of Assessment	Results	Adverse Effects Reported
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	Exercise test on a bicycle ergometer and 6-minute walking test at baseline, repeated at 4, 8, 12, and 24 weeks. Clinical status, including NYHA class, assessed during each visit.	Cilazapril vs Captopril: Increase in exercise duration (seconds) from baseline to week 12: 62.7 ± 0.06 vs 73.1 ± 2.4 (NS) From baseline to week 24: 81.2 ± 2.2 vs 80.3 ± 3.5 (NS) Increase in distance in 6-minute walk test from baseline to week 12: 33 ± 4 vs 30 ± 6 From baseline to week 24: 44 ± 5 vs 35 ± 8 Improvement by at least one NYHA class at 24 weeks: 35% vs 36% (NS)	Cilazapril vs Captopril: Patients reporting one or more adverse events at week 12 41.6% vs 40.7%; at week 24 52.5% vs 54.6% Most frequent dizziness (10.0% vs 10.2%) and coughing (9.0% vs 9.3%). For captopril, elderly patients had more adverse events (63.0%) than younger patients (48.4%); cilazapril no difference by age group. Withdrawals due to adverse effects 5.4% vs 13.0% 8 deaths (0.8% placebo, 2% cilazapril, 1.8% captopril)

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
de Graeff 1989 The Netherlands Open Single center (Poor)	7 Ramipril 5 Captopril	A: Ramipril 5 mg initially, then after 24 hours 10 mg once daily unless symptomatic hypotension occurred; when clinical response unsatisfactory, dose adjusted to maximum of 10 mg BID. B: Captopril 12.5 mg initially, then after 24 hours 25 mg TID unless symptomatic hypotension occurred; when clinical response unsatisfactory, dose adjusted to maximum of 50 mg TID. 12 weeks	Hospitalized patients with chronic HF NYHA Class III-IV, with severe restriction of physical activity or symptoms of dyspnea or fatigue at rest for more than 3 months despite adequate treatment with salt restriction, diuretics, and digoxin.
Dirksen 1991 The Netherlands Open Multicenter (Poor)	19 Enalapril 21 Captopril	A: Enalapril 10 mg once daily for 2 weeks, then depending on response, either maintained, decreased to 5 mg once daily or increased to 20 mg once daily. B: Captopril 12.5 mg TID for 2 weeks, then depending on response, maintained, decreased to 6.5 mg TID or increased to 25 mg TID. 3 months	NYHA Class II or III.

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Allowed other medications/ interventions	Age Gender Ethnicity	Baseline NYHA Class	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
de Graeff 1989 The Netherlands Open Single center (Poor)	Treatment with salt restriction, diuretics, and digoxin was maintained.	Ramipril vs Captopril: mean age 70 (62-76) vs 58 (48-81) 86% vs 100% males Ethnicity NR	Ramipril vs Captopril: Class III: 29% vs 60%, Class III-IV: 43% vs 40% Class IV: 29% vs 0%	# screened NR # eligible NR 13 enrolled	1 withdrew 12 analyzed
Dirksen 1991 The Netherlands Open Multicenter (Poor)	Other cardiovascular agents except digitalis, diuretics, and sublingual nitroglycerin discontinued at start of run-in. Doses not altered. Treatment with potassium-sparing diuretics not allowed during treatment.	Enalapril vs Captopril: Mean age 61 (range 31-77) vs 61 (range 46-74) 68% vs 76% males Ethnicity NR	Enalapril vs Captopril: Class II: 58% vs 48% Class III: 42% vs 52%	# screened NR 52 eligible 40 enrolled	0 withdrew 0 lost to followup 40 analyzed

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Method of Outcome Assessment and Timing of Assessment	Results	Adverse Effects Reported
de Graeff 1989 The Netherlands Open Single center (Poor)	Patients were initially hospitalized, discharged after reaching a clinically stable condition and seen every 3 weeks as outpatients. Symptoms evaluated using the NYHA score.	Ramipril vs Captopril, Improvement by at least 1 NYHA Class: 58% vs 40%	3 deaths (2 Ramipril, 1 Captopril) 1 patient not analyzed- found to have hyperthyroidism after 6 weeks of Captopril. 1 patient (Ramipril) discontinued after 1st dose due to catheter sepsis. 1 patient (Captopril withdrawn after 9 weeks because of progression of heart failure. 3 patients developed symptomatic hypertension with dizziness, blurred vision, and sleepiness (2 Ramipril, 1 Captopril) 1 Patient (Captopril) developed itching and mild rash.
Dirksen 1991 The Netherlands Open Multicenter (Poor)	NYHA class measured at week -2, -1, 0, 2, 4, 6, 8, 10, 12, and bicycle ergometric tests at weeks 0, 2, 12.	Enalapril vs Captopril, NYHA Class at week 12: Class I 16% vs 14% Class II 63% vs 57% Class III 21% vs 19% Class IV 0% vs 10% Improvement from baseline statistically significant (p=0.02) only in Enalapril group Improvement by at least 1 class: 37% vs 33%	Enalapril vs Captopril: Drug-related adverse effects: 17 vs 16 events worsening of NYHA class 0% vs 10%

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Gavazzi 1994 Italy Multicenter (Fair)	76 Quinapril 70 Captopril	A: Quinapril 10 mg once daily, after 4 weeks of treatment, doses titrated to 20 mg once daily as required to maintain adequate BP control without sitting BP falling below 110/70 or other major adverse events. B: Captopril 25 mg BID, after 4 weeks of treatment, doses titrated to 50 mg BID as required to maintain adequate BP control without sitting BP falling below 110/70 or other major adverse events. 12 weeks	Over age 40 with Class I-III HF
Giles 1988, 1989 US Multicenter (Fair)	94 Lisinopril 95 Captopril Subgroup of patients over age 65: 37 Lisinopril 28 Captopril	A: Lisinopril 5 mg once daily, increased if needed at 4-week intervals unless symptomatic hypotension occurred. Titration doses 5 mg, 10 mg, 20 mg once daily. B: Captopril 12.5 mg TID, increased if needed at 4-week intervals unless symptomatic hypotension. Titration doses 12.5 mg, 25 mg, 50 mg TID. 12 weeks	Age 18 or older, NYHA Class II, II, or IV, able to exercise 1-12 minutes on a treadmill.

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Allowed other medications/ interventions	Age Gender Ethnicity	Baseline NYHA Class	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
Gavazzi 1994 Italy Multicenter (Fair)	Any baseline diuretic and/or digitalis therapy was maintained at the same dose during washout and treatment period.	Captopril vs Quinapril Mean age 59.9 (sd 9.0, range 41-79) vs 62.2 (sd 7.9, range 47-79) 73% vs 75% males	Captopril vs Quinapril Class I: 23% vs 12% Class II: 50% vs 72% Class III 27% vs. 14%	# screened NR # eligible NR # enrolled NR	# withdrawn NR # lost to followup NR 146 analyzed
Giles 1988, 1989 US Multicenter (Fair)	All antihypertensive and vasodilator medications withdrawn. Doses of digoxin were maintained constant throughout the study period. Doses of diuretics could be adjusted for clinical reasons during the study.	Lisinopril vs Captopril Mean age 61.3 vs. 59.1 76% vs. 81% male, 24% vs 29% black In sub-analysis of those > age 65 (Giles 1988): Mean age 71 vs 70 81% vs 82% male Ethnicity NR	Lisinopril vs Captopril Class II 31% vs 31% Class III 61% vs 62% Class IV 8% vs 7%	# screened NR # eligible NR 189 enrolled	# withdrawn NR # lost to followup NR 189 analyzed

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Method of Outcome Assessment and Timing of Assessment	Results	Adverse Effects Reported
Gavazzi 1994 Italy Multicenter (Fair)	Clinical signs and symptoms, exercise capacity, EKG, all performed at end of washout and during week 12 of treatment. Classification of HF by NYHA criteria determined by investigators at each clinical visit.	Captopril vs Quinapril Improvement in NYHA class 27.1% vs 24.0% (NS) Increase in exercise duration, baseline to week 12: 451.7 to 519.0 sec vs 422.1 to 497.2 sec (p < 0.05 for both Captopril and Quinapril) Improvement in symptoms at 12 weeks Captopril vs Quinapril Any sign of HF 27.1% vs 41.3% (NS) dsypnea at rest 45.4% vs 80.0% (NS) dsypnea at effort 40.9% vs 39.2% (NS) orthopnea 66.7% vs 50.0% peripheral edema 61.1% vs 72.0% (NS) lung congestion 57.1% vs 86.4% (p=0.03)	Captopril: 12 adverse events in 9 patients vs Quinapril 11 adverse events in 9 Quinapril patients 7 vs 5 considered drug-related Most frequent drug-related adverse event was hypotension (3 Captopril vs 2 Quinapril)
Giles 1988, 1989 US Multicenter (Fair)	Treadmill exercise tests: 2 during baseline and 23 (at 4-week intervals) during study. Lab screening at baseline and 4-week intervals. Clinical evaluation at 4-week intervals and 2 weeks after each dose adjustment	Lisinopril vs Captopril Change in NYHA Class 30% vs 31% improved 0% vs 3% deteriorated Mean increase in exercise duration at week 12 137 sec vs 120 sec (p=NS) Subgroup of patients over age 65 (Giles 1988): Lisinopril vs Captopril Change in NYHA Class 24% vs 26% improved, 76% vs 74% unchanged, 0% vs 0% worse (p NR) Mean change in exercise duration 134.3 sec vs 71.8 sec (p=0.08)	35.1% of L and 47.4% of C had clinical adverse experiences (p=NS). 3 C died, 0L died. 11.6% of C and 3.2% of L had serious adverse effects. 2 patients in each group had adverse effects considered severe and/or requiring discontinuation of therapy: Symptomatic dizziness requiring discontinuation of therapy occurred in 1 patient in each group. Captopril Discontinued in 1 patients due to severe taste disturbance, and Lisinopril discontinued in 1 patient due to worsening hepatic and renal function. Subgroup analysis: L- 51%, C- 54% had 1 or more AE; serious AE: L- no deaths, 1 GI pain; C- 1 death, 1 hypotension, 1 cerebrovascular disease, 1 hypertensive crisis

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Haffner 1995 UK Multicenter (Poor)	41 Captopril 39 Enalapril	A: Captopril 12.5 mg BID B: Enalapril 2.5 mg BID 6 months	Over age 65, heart failure defined by 2 or more: Tachycardia, gallop rhythm, increased jugular vein pressure, bilateral basal crepitations or auscultaton of the lungs, peripheral edema, and or evidence of heart failure on chest x-ray. Required 40-80 mg frusemide daily.

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Allowed other medications/ interventions	Age Gender Ethnicity	Baseline NYHA Class	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
Haffner 1995 UK Multicenter (Poor)	Not clear, frusemide allowed; decreased to 40 mg if dose was 80 mg	Captopril vs Enalapril Mean age 77 (66-93) vs 75.3 (65-93) Sex NR Ethnicity NR	NYHA Class NR. Clinical signs, Captopril vs Enalapril: Tachycardia 39% vs 54% Gallop rhythm 66% vs 79% Raised jugular vein pressure 32% vs 44% Pulmonary edema 76% vs 69% Edema 58% vs 49%	# screened NR 96 eligible 80 enrolled	24 withdrawn 0 lost to followup 56 analyzed

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Method of Outcome Assessment and Timing of Assessment	Results	Adverse Effects Reported
Haffner 1995 UK Multicenter (Poor)	Baseline assessments: BP and pulse, blood tests, ECG, chest X-ray, exercise test, symptom-oriented questionnaire, hemodynamic tests, blood test, and questionnaire repeated at 1 week; further complete assessments at 3 and 6 months. Patients were visited monthly to deliver meds and assess compliance by tablet count. Walking test in 25 patients at one center. Quality of life and minor adverse effects assessed by questionnaire at one center.	Walking tests (performed on 25 patients only) improvement in both groups after 3 months. Trend to further improvement at 6 months in Captopril group (0.54 m/s, sd 0.14) but not in Enalapril group (0.49 m/s, sd 0.28). Differences between groups NS, p NR	By questionnaire (of 45 patients only)- GI complaints 9/14 Enalapril (64%) vs 2/14 Enalapril (11%), p=0.039 30% (24/80) patients withdrawn after randomization. Reasons for withdrawal, Captopril vs Enalapril death (sudden) 3(1) vs 3(3) ineffective 2 vs 1 poor compliance 1 vs 1 symptomatic hypotension 0 vs 4 other adverse effects 5 vs 0 anemia 1 vs 0 on non-permitted drug 1 vs 0 cardiac surgery 0 vs 1 proteinuria 0 vs 1 renal impairment 0 vs 1 patient request 0 vs 1 cough 0 vs 1 total events 13 vs 14

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Morisco 1997 Italy Multicenter (Fair)	128 Lisinopril 123 Captopril	A: Lisinopril 5 mg once daily increased to 10 mg after 2 weeks if SBP >90, no symptoms of hypotension, and if need for additional therapeutic effect, increased to 20 mg after 2 weeks if above criteria met. Dose decreased if symptomatic hypotension or any other drug-related adverse effects. B: Captopril 12.5 mg once daily, increased to 12.5 mg BID after 2 weeks if SBP >90, no symptoms of hypotension, and if need for additional therapeutic effect, then increased to 25 mg BID after 2 weeks if above criteria met. Dose decreased if symptomatic hypotension or any other drug-related adverse effects. 12 weeks	Ages 65-80, NYHA Class II or III, EKG evidence of LVEF <45%, in sinus rhythm, on stable doses of diuretics, capable of 3-12 minutes of exercise.
Packer 1986 US Single center Open (Poor)	21 Captopril 21 Enalapril	A: Captopril 50 mg TID. B: Enalapril 20 mg BID. 12 weeks	Patients with severe HF (persistent dyspnea or fatigue at rest or during minimal exertion, despite treatment with digitalis and diuretics; LVEF <30%).

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Allowed other medications/ interventions	Age Gender Ethnicity	Baseline NYHA Class	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
Morisco 1997 Italy Multicenter (Fair)	Loop diuretics, long-acting nitrates, amiodarone, anticoagulants allowed. Treatment with potassium-sparing agents, digitalis glycosides, calcium-channel blockers, beta-blockers, vasodilators, all antihypertensive medications withdrawn.	Lisinopril vs Captopril: Mean age 69 (sd0.5) vs 70 (sd 0.5) 80% vs 75% males Ethnicity NR	Lisinopril vs Captopril: Class II: 70% vs 74% Class III: 30% vs 26%	# screened NR 271 eligible 251 enrolled	37 withdrawn 0 lost to followup 214 analyzed
Packer 1986 US Single center Open (Poor)	Maintenance treatment with oral digitalis, diuretics kept constant, salt-restricted diet continued, previously prescribed vasodilators discontinued, no maintainance treatment with oral potassium supplements, potassium-sparing diuretics, or direct-acting vasodilators	Captopril vs Enalapril Mean age 59 (sd 2.9) vs 62.2 (sd 3.0) 90% vs 76% males Ethnicity NR	Baseline NYHA class NR; Cause of heart failure, Captopril vs Enalapril: Ischemic heart disease 57% vs 71% Primary dilated cardiomyopathy 29% vs 29% Primary valvular disease 14% vs 29%	# screened NR # eligible NR 42 enrolled	0 withdrawn 0 lost to followup 42 analyzed

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Method of Outcome Assessment and Timing of Assessment	Results	Adverse Effects Reported
Morisco 1997 Italy Multicenter (Fair)	Physical exam and symptom review at recruitment and at each visit. Exercise test (bicycle) at 6 and 12 weeks and baseline.	NYHA Class, Lisinopril vs Captopril 37.8% vs 36.9% improved 61.2% vs 60.2% no change 1% vs 2.9% deteriorated changes similar in both groups (no p-values reported). Improvement in signs and symptoms similar (third heart sounds, jugular venous distension, rales, edema, orthopnea, dyspnea)	Volunteered adverse effects obtained at each visit. Captopril: 20 patients withdrew, 5 for adverse effects, Lisinopril: 17 withdrew, 8 for adverse effects (p=NS) 2 Captopril, 0 Lisinopril died 11.4% of Captopril vs 14.1% of Lisinopril had adverse effects not leading to withdrawal Adverse effects leading to withdrawal, Captopril vs Lisinopril hypotension 1 vs 2, hypertension 1 vs 0, fatigue 1 vs 0, rash, pruritis 1 vs 1, vomiting 1 vs 0, icterus 0 vs 1, abdominal pain 0 vs 1, dyspnea 0 vs 1, renal dysfunction 0 vs 2.
Packer 1986 US Single center Open (Poor)	Not clear- discussion of hemodynamics, but not clinical assessment.	Improvement by at least 1 NYHA class: Captopril 71% vs Enalapril 52 % Captopril: 29% did not benefit clinically (1 died suddenly of ventricular tachycardia) vs Enalapril: 48% did not benefit clinically (1 died of GI bleeding)	Captopril: 10 patients episodic dizziness (1 syncope), 1 patient rash, 1 patient dysguesia, 5 patients increase in blood urea nitrogen (azotemia) Enalapril: 11 patients episodic dizziness (6 had syncope or near syncope), worsening azotemia in 9 patients; 2 patients symptomatic hypotension after 1st dose, 1 patient severe dizziness and chest pain4 hours after 1st dose; 1 patient developed severe symptomatic hypotension after 6 weeks of Enalapril.

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Zannad 1992 France Multicenter (Poor)	138 Lisinopril 140 Enalapril	B: Lisinopril 2.5 mg single dose, then 5 mg once daily for 2 weeks, then if needed and tolerated 5 mg once daily for 4 weeks, then 10 mg once daily if needed to 12 weeks. Dose decreased at any point if hypotension or adverse effects. A: Enalapril 2.5 mg single dose, then 5 mg once daily for 2 weeks, then if needed and tolerated 5 mg once daily for 4 weeks, then 10 mg once daily if needed to 12 weeks. Dose decreased at any point if hypotension or adverse effects. 12 weeks	Over age 21 with NYHA Class II or III, on optimal dose of digitalis and/or diuretics and capable of 4-12 minutes of exercise protocol; underlying cause of HF not used to judge eligibility.
Zannad 1998 France (Fair)	122 Fosinopril 132 Enalapril	A: Fosinopril 5 mg once daily for 2 weeks, then 10 mg once daily for 4 weeks, then 20 mg once daily for up to 12 months (all if no decrease in BP) B: Enalapril 5 mg once daily for 2 weeks, then 10 mg once daily for 4 weeks, then 20 mg once daily for up to 12 months (all if no decrease in BP). 12 months	Ages 18-85, stratified to include at least 1/3 over age 65, NYHA Class II or III and LVEF <40% ; receiving diuretics.

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Allowed other medications/ interventions	Age Gender Ethnicity	Baseline NYHA Class	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
Zannad 1992 France Multicenter (Poor)	Before randomization, 10-14 day placebo period in which digoxin and/or diuretic doses optimized, all other vasodialator and ACE Inhibitor treatment withdrawn. Digoxin and/or diuretics maintained throughout study, potassium supplements reported if hypokalemia developed. No potassium-sparing diuretics, nitroglyerin permitted, anticoagulant treatment permitted.	Lisinopril vs Enalapril mean age 63 (sd 10, range 26-84) vs 61 (sd 10, range 28-80) 86% vs 81% male Ethnicity NR	Lisinopril vs Enalapril: Class II: 58% vs 64% Class III: 42% vs 36%	# screened NR 300 eligible NR 278 enrolled	29 withdrawn # lost to followup NR 249 analyzed
Zannad 1998 France (Fair)	Diuretics, diltiazem, nitrates, digitalis allowed.	Fosinopril vs Enalapril: Mean age 63.3 (sd 9.2, range 35-79) vs 63.6 (sd 10.7, range 23-70) 81% vs 75% male Ethnicity NR	Fosinopril vs Enalapril: Class II: 84% vs 80% Class III: 16% vs 20%	296 screened 280 eligible 254 enrolled	94 withdrawn # lost to followup NR 254 analyzed

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Method of Outcome Assessment and Timing of Assessment	Results	Adverse Effects Reported
Zannad 1992 France Multicenter (Poor)	Exercise test at baseline, 6 and 12 weeks, Holter monitor at baseline and week 12, blood chemistry at entry, 2,4,6,12 weeks; adverse events volunteered at each visit.	Lisinopril vs Enalapril: NYHA Class at 12 weeks: 48% improvement vs 43% improvement 49% no change vs 53% no change 3% deterioration vs 2% deterioration (All p= NS) Symptoms: Both drugs improved monitored symptoms, and effects of treatment similar for groups Mean increase in exercise duration at 6 weeks: 30.1 sec vs 13.5 sec (p=0.1415) Mean increase in exercise duration at 12 weeks: 65.1 sec vs 41.9 sec (p=0.0748)	No significant differences with respect to incidence of spontaneously reported symptoms, side effects, or withdrawals from treatment.
Zannad 1998 France (Fair)	Rate of death and hospitalization for worsening HF, time to first critical event (event-free survival time), change in NYHA class, cardiac symptoms and signs; 12 months of followup.	Fosinopril vs Enalapril: Death 1.6% vs 4.6% Withdrawal for worsening HF 4.9% vs 7.6% Hospitalization for worsening HF 0.8% vs 3.0% Supplementary frusomide or emergency department for worsening HF 4.9% vs 5.3% None of the above 12.2% vs 20.5% (p=0.059) Total hospitalization and death 19% vs 25% (p=0.28) Event-free survival time 1.6 vs 1.0 months (p=0.032)	

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Zebrah Study Group (Adgey) 1993 UK Multicenter (Fair)	127 Lisinopril 124 Enalapril	A: Lisinopril 5 mg once daily, increased to 10 mg then 20 mg if SBP >90, no symptoms of hypotension and no clinical reason not to increase the dose. B: Enalapril 5 mg once daily, increased to 10 mg then 20 mg if SBP >90, no symptoms of hypotension and no clinical reason not to increase the dose. 6 months	Over age 18 with NYHA Class III or IV confirmed by clinical signs or symptoms and LVEF <35%, capable of at least 1 minute of exercise test and in sinus rhythm or controlled atrial fibrillation.

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Allowed other medications/ interventions	Age Gender Ethnicity	Baseline NYHA Class	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
Zebrah Study Group (Adgey) 1993 UK Multicenter (Fair)	Current diuretic and/or digoxin treatment optimized and kept constant 2 weeks before treatment. Concurrent treatment with anti-coagulants, anti-arrhythmics, or vasodilator drugs permitted but had to remain constant during the study or patient was withdrawn. Occasional sublingual GTN, taken as required, was permitted. Medication for conditions other than Heart f was recorded and kept constant if possible.	Lisinopril vs Enalapril: Mean age 62.4 vs 62.9 79% vs 82% male Ethnicity NR	Lisinopril vs Enalapril: Class III: 80% vs 82% Class IV: 20% vs 18%	# screened NR # eligible NR 251 enrolled	68 withdrawn # lost to followup NR 194 analyzed

Evidence Table 9. Head-to-head trials of ACEIs for heart failure

Author Setting Country (Quality)	Method of Outcome Assessment and Timing of Assessment	Results	Adverse Effects Reported
Zebrah Study Group (Adgey) 1993 UK Multicenter (Fair)	Exercise stress test at visit 1, at visit 2, baseline exercise test, LVEF measured, NYHA Class recorded, abbreviated symptom review and physical exam. At subsequent visits (timing not clear), adverse events, abbreviated symptom review, physical exam. Final visit at 6 months: all measurements, exercise test, NYHA class, LVEF, chest x-ray.	Lisinopril vs Enalapril: NYHA Class at 6 months: Class I: 8% vs 6% Class II: 51% vs 59% Class III: 38% vs 32% Class IV: 3% vs 2% Improvement by one or more class: 68% vs 70% (p=NS)	Lisinopril vs Enalapril Most common adverse effects: Dizziness 37 vs 45 Cough 15 vs 18 Dry cough 13 vs 15 Headache 7 vs 19 Tiredness 8 vs 12 Diarrhea 11 vs 6 Nausea 6 vs 8 Syncope 5 vs 7 Confusion 3 vs 7

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Score (good/ fair/ poor)	Comparison	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population
Acanfora 1997 Italy	Fair	Quinapril vs Captopril	Method not described	Not reported	Yes	Similar
Bach 1992 Germany, Italy	Poor	Lisinopril vs Captopril	Computer-generated	Not reported	Yes	Similar
Beynon 1997	Poor	Captopril vs Quinapril	Method not described	No, open	Yes	Similar, although single center

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Acanfora 1997 Italy	MI or revascularization surgery in previous 3 months; angina at rest or intermittent cladication; CV events in previous 6 months, chronic bronchopulmonary disease, atrial fibrillation or severe arrhythmias, fixed heart pacemakers, hemodynamically significant aortic or mitralic stenosis, significant renal or hepatic failure, hemopoietic or endocrine diseases; SBP 90 or lower or 190 or higher, hypersensitivity or other contraindicatio nof ACE inhibitors, potassium < 3 or >5.5, receiving treatment with potassium-sparing diuretics, positive inotropic drugs (except digoxin), allopurinol, cytostatic, immunosuppressants, beta-blockers, calcium antagonists, vasodilators, other ACE inhibitors.	Yes	Yes	Not reported	Yes	Not clear; states "complete data were available for 131 patients."
Bach 1992 Germany, Italy	Recent history of MI or cardiac surgery, cerebrovascular accident, clinically important renal disorders, right heart failure, lung disease limiting exercise tolerance, drug or alcohol abuse.	Yes	Yes	Not reported	Yes	No- completers analysis and per protocol analysis
Beynon 1997	Acute HF or rapidly deteriorating status, hepatic or renal dysfunction, MI within 6 weeks, unstable angina, or other disease precluding survival, etc, p 585 table.	Yes	No	Not reported	No	Yes, but Table IV is not ITT, check text and report results of ITT

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Funding	Control group standard of care?	Length of follow-up
Acanfora 1997 Italy	Yes	Yes	2 dropped due to adverse effects, both Captopril, 0 Quinapril.	Not reported	Yes	12 weeks
Bach 1992 Germany, Italy	84% (125/148) lisinopril vs 91% (127/139) captopril completed	Yes	Yes- more lisinopril withdrew, high withdrawal. 315 entered, 28 withdrew at runin, 38 withdrew during treatment (total 66/315=21%)	Not reported	Yes	12 weeks
Beynon 1997	Not sure	Yes	Yes- 48% of captopril avs 37% of quinapril withdrew	Supported by grant from Parke Davis	Yes	16 weeks after 2 to 8 weeks titration

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Score (good/ fair/ poor)	Comparison	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	Fair	Cilazapril vs Captopril	Method not described	Not reported	Cilazapril lower score on 2 measures at baseline, no statistical test reported.	Similar
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	Fair	Cilazapril vs Captopril	Method not described	Not reported	Yes	Similar
de Graeff 1989 Tbe Netherlands	Poor	Ramipril vs Captopril	Method not described	No, open	7 ramipril, 6 captopril patients- appear similar, no statistical tests reported	Similar

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	Myocardial infarction or stroke within previous 3 months, surgery for primary valvar disease, a pacemaker, or systolic blood pressure <90 mm Hg.	Yes	Yes	Not reported	Yes	No- only analyze results on patients with complete data
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	MI or cerebral stroke in past 3 months, surgery for primary valvular disease or pacemaker implantation indicated, systolic blood pressure <90 mm Hg or other clinically significant disease.	Yes	Yes	Not reported	Yes	Unable to determine.
de Graeff 1989 Tbe Netherlands	Acute myocardial infarction or unstable angina pectoris within the preceding 6 weeks, SBP 90 or less, severe valvular disease and creatinin clearance less than 30ml/min.	Yes	No	Not reported	No	individual results reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Funding	Control group standard of care?	Length of follow-up
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	Not sure	Attrition yes, others no.	18% with no followup data-not reported by group	Supported by grant from Hoffmann-LaRoche, Switzerland	Yes	24 weeks
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	Unable to determine	Attrition yes, others no.	Not reported	Not reported; authors who prepared and analyzed data were from Hoffmann-LaRoche.	Yes	24 weeks
de Graeff 1989 Tbe Netherlands	Yes	Yes	only 8/12 completed (67%)	not reported	Yes	12 weeks

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Score (good/ fair/ poor)	Comparison	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population
Dirksen 1991	Poor	Enalapril vs Captopril	Method not described	No, open	Yes	Similar
Gavazzi 1994 Italy	Fair	Quinapril vs. Captopril	Method not described	Not reported	Higher prevalence of NYHA Class II in quinapril ($p<0.05$), otherwise yes	Similar
Giles 1988, 1989 US	Fair	Lisinopril vs Captopril	Method not described	Not reported	Yes	Excluded those with history of captopril intolerance
Haffner 1995 UK	Poor	Captopril vs Enalapril	No	Not reported	Yes	No? Withdrawn if poor compliance, decreased cardiac function, severe adverse effects, death.

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Dirksen 1991	Hypotension (SBP <60), acute HF or MI within 2 months, cerebrovascular accident within 6 months	Yes	No	not reported	No	Those withdrawing at run-in not evaluated
Gavazzi 1994 Italy	After washout, if systolic BP <110 or diastolic BP <70, creatinine concentration 221 or more.	Yes	Yes, not for washout	not clear	Yes	Yes
Giles 1988, 1989 US	History of captopril intolerance, recent unstable angina, MI, or cerebrovascular accident, clinically important renal, hepatic, or hematologic disorders, hyper- or hypokalemia cor pulmonale, aortic valvular heart disease, sytolic BP < 80, substance abuse.	Yes	Yes	Not reported	Yes	Yes, but not for subgroup of those over age 65.
Haffner 1995 UK	SBP >190 or <110; serum creatinine >300, clinical signs of aortic or mitral stenosis or cor pulmonale.	Yes	Yes	not reported	Yes	No

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Funding	Control group standard of care?	Length of follow-up
Dirksen 1991	Yes	Yes	12/52 (23%) withdrawn at run-in, not reported breakdown by drug- 19 enalapril and 21 captopril received treatment	Not reported	No	12 weeks
Gavazzi 1994 Italy	yes?	yes	11.4% of Captopril and 10.5% of Quinapril withdrew	supported by grant from Parke-Davis	Yes	12 weeks
Giles 1988, 1989 US	Final doses- lisinopril vs captopril: low 35% vs 21%, medium 27% vs 29%, high 38% vs 50%	Yes	11% in each group withdrew due to adverse effects	Supported in part by Merck Sharp and Dohme, some investigators from Merck Sharp and Dohme	Yes	12 weeks
Haffner 1995 UK	Not sure	yes	High loss- 96 entered, 16 ineligible at run-in (17%), 24 more withdrawn (total loss=42%: 40/96); 30 withdrew after randomization	Supported by Bristol-Myers Squibb	Yes	6 months

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Score (good/ fair/ poor)	Comparison	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population
Morisco 1997	Fair	Lisinopril vs captopril	Method not described	Not reported	Yes	Yes, but limited to elderly patients
Packer 1986 US	Poor	Captopril vs Enalapril	Computer-generated	not described	Yes	Patients with severe HF, persistent symptoms despite digitalis and diuretics
Zannad 1992 France	Poor	Lisinopril vs Enalapril	Method not described	Not reported	Mean exercise capacity at end of run-in lisinopril vs enalapril: 433 (sd 119) vs 462 (sd 141) (p=NS); significant difference before run-in	similar
Zannad 1998 France	Fair	Fosinopril vs Enalapril	Method not described	Not reported	Yes	similar

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Morisco 1997	MI or cardiac surgery (including PTCA) in last 3 months, stable or unstable angina, cerebrovascular accident in previous 6 months, intermittent claudicaiton, right heart failure, severe pulmonary disease limiting exercise performance, atrial fibrillation, arryhtmias requiring treatment other than amiodarone, fixed rate prcemakers, significant aortic or mitral valve stenosis or regurgitation, clinically relevant renal, hepatic, endocrine, or hematological disorders SBP <90 or >160, history of ACE inhibitor intolerance, hyper- or hypokalemia, receiving other investigational treatment, alcohol abuse.	Yes	Yes	Not reported	Yes, double dummy	Yes
Packer 1986 US	Not reported	yes	No	not reported	No	Yes?
Zannad 1992 France	Recent history of MI or cardiac surgery, or clinically important renal disease, lung disease, angina limiting exercise capacity, arrhythmias requiring treatment other than digoxin or amiodarone, known sensitivity or contraindication to ACE inhibitors.	Yes	Yes	Not reported	Yes	No- 'completers analysis'
Zannad 1998 France	Symptoms of unstable angina in past 1 month, MI past 3 months, obstructive cardiac valvular disease and cardiomyopathy, BP < 90, severe liver disase, renal dysfunction.	Yes	Yes	Not reported	Yes	Yes

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Funding	Control group standard of care?	Length of follow-up
Morisco 1997	Dose at end: lisinopril vs captopril: 48.5% vs 50.4% low, 27% vs 25.4% medium, 24% vs 24.2% high	Yes	20/271 withdrew at run-in (7%); 20/123 (16.3% of captopril nd 17/128 lisinopril (13.2%) withdrew	Not reported	Yes	12 weeks
Packer 1986 US	Yes	Yes	No	Supported by NIH/NHLBI	No, not titrated (for either group)	12 weeks
Zannad 1992 France	Yes	Yes	22/200 withdrew at run-in (7%), 29 during treatment (total 17% withdrawal) 15 enalapril and 14 lisinopril withdrew, # randomized in each group not given	Not reported	No	12 weeks
Zannad 1998 France	?	Yes	23% of fosinopril and 26.5% of enalapril discontinued due to adverse effects, including worsening heart failure	Sponsored by Bristol-Myers-Squibb as part of development plan for fosinopril	Yes	12 months

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Score (good/ fair/ poor)	Comparison	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population
ZEBRAH (Adgey) 1993	Fair	Lisinopril vs Enalapril	Method not described	Not reported	Yes	Similar- withdrawn if first-dose hypotension.

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
ZEBRAH (Adgey) 1993	MI, cardiac surgery or PTCA in previous 3 months, unstable angina or severe angina limiting exercise, CVA in past 6 months, right heart failure due to lung disease, lung disease limting exercise performance, uncontrolled arrhythmias, hemodynamically significant aortic stenosis. Clinically relevant renal diseae or serum creatinine >150, clinically significant hemopoietic or endocrine disorders (except controlled diabetes mellitus), bilateral renal artery stenosis, constrictive pericarditis or SBP <80, known hypersensitivity or contraindication to ACE inhibitors, or recent history of drug or alcohol abuse or poor compliance; women of childbearing potential.	Yes	Yes	Not reported	Yes	No

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Funding	Control group standard of care?	Length of follow-up
ZEBRAH (Adgey) 1993	?	Yes	High overall loss: 30/127 (24%) Lisinopril 30/124 (24%) Enalapril	Zeneca provided financial and logistical support.	Yes	6 months

Evidence Table 11. Results of systematic review of placeb-controlled trials of ACEIs for
Results of systematic review of placeb-controlled trials of ACEIs for heart failure
(From Garg 1995)

Intervention	Study	Number of Patients	Total Mortality (Odds Ratio)	95% CI	Mortality or Hospitalization (Odds Ratio)	95% CI
Benazepril	Colfer et al.	172	0.05	0-0.55	0.22	0.04-1.22
	McGarry	61	2.21	0.22-22.15	0.90	0.25-3.31
	Summary	**233**	**0.36**	**0.07-1.90**	**0.54**	**0.19-1.52**
Captopril	Magnani	494	1.14	0.35-3.64	--	--
	Bussman	23	0.55	0.08-3.83	--	--
	Captopril Digoxin Multicenter	204	1.18	0.56-2.49	0.82	0.45-1.50
	CMRG	105	0.20	0.06-0.65	0.19	0.06-0.59
	Barabino	101	0.52	0.22-1.22	0.32	0.14-0.70
	Kleber	170	1.07	0.54-2.11	0.94	0.51-1.72
	Summary	**697**	**0.79**	**0.54-1.14**	**0.61**	**0.43-0.87**
Cilazapril	Drexler	21	0.12	0-6.20	0.89	0.11-7.51
	Summary	**21**	**0.12**	**0-6.20**	**0.89**	**0.11-7.51**
Enalapril	Cleland	20	(0 deaths)			
	Rucinska	132	0.48	0.09-2.48	0.48	0.09-2.48
	CONSENSUS	253	0.56	0.34-0.91	0.89	0.51-1.57
	Enalapril CHF Investigators	256	0.57	0.19-1.66	0.51	0.18-1.45
	Dickstein	41	0.14	0-7.16	0.12	0.02-0.93
	SOLVD	2569	0.82	0.70-0.97	0.68	0.59-0.80
	Rucinska	110	0.14	0-6.82	0.14	0.00-6.82
	Summary	**3381**	**0.78**	**0.67-0.91**	**0.68**	**0.59-0.79**
Lisinopril	Zwehl	275	0.83	0.19-3.67	0.83	0.19-3.67
	Giles	193	0.34	0.08-1.40	0.27	0.07-1.05
	Rucinska	58	7.94	0.16-400.92	1.07	0.07-17.61
	Gilbert	20	(no deaths)			
	Summary	**546**	**0.62**	**0.23-1.67**	**0.50**	**0.19-1.27**
Perindopril	Lechat	125	0.14	0-7.16	0.14	0.01-2.26
	Summary	**125**	**0.14**	**0-7.16**	**0.14**	**0.01-2.26**
Quinapril	Riegger	225	(no deaths)	--	--	--
	Northridge	32	(no deaths)	--	--	--
	Uprichard	224	0.49	0.05-4.78	0.49	0.05-4.78
	Uprichard	208	0.65	0.11-3.83	0.65	0.11-3.83
	Uprichard	186	3.84	0.16-94.01	3.84	0.16-94.01
	Summary	**875**	**0.79**	**0.22-2.85**	**0.79**	**0.22-2.85**
Ramipril	Swedberg	223	0.41	0.11-1.44	0.42	0.17-1.01
	Maass	132	1.40	0.30-3.61	1.04	0.30-3.61
	Gordon	192	0.27	0.05-1.34	0.25	0.08-0.81
	Maass	500	0.82	0.26-2.63	0.58	0.25-1.38
	Maass	95	1.02	0.06-16.58	0.67	0.11-4.04
	Lemarie	85	7.57	0.15-381.49	0.75	0.16-3.51
	Summary	**1227**	**0.67**	**0.36-1.24**	**0.52**	**0.33-0.83**
All ACE Inhibitors	**Summary**		**0.77**	**0.67-0.88**	**0.65**	**0.57-0.74**

Evidence Table 12. Adverse effects reported in head-to-head trials of placebo-controlled trials of ACEIs for recent myocardial infarction

Study Year	Interventions	Significant hypotension	Cough	Angioedema	Significant renal failure	Overall withdrawals	Withdrawal due to adverse events
Head-to-head trials of one included ACEI vs. another included ACEI							
Foy 1994	A: Captopril B: Enalapril	NR	8% 5%	NR	NR	24% 16%	Not clear
Lau 2002	A: Captopril B: Perindopril	7% 2%	5% 3%	NR	NR	14% 9%	NR
Trials of an included ACEI vs. placebo							
Trials of Captopril vs. placebo							
ISIS-4 1995	A: Captopril B: Placebo	10% 5%	NR	NR	1.1% 0.6%	NR	NR
Kingma (CATS) 1994	A: Captopril B: Placebo	27% 18%	NR	NR	NR	NR	NR
Kleber (ECCE) 1997	A: Captopril B: Placebo	37% 18%	NR	NR	NR	4% 12%	Not clear ('severe' adverse events 17% vs. 17%)
Kober (TRACE) 1995	A: Captopril B: Placebo	31% 22%	34% 21%	NR	14% 11%	37% 36%	Not clear
CCS-1 1997	A: Captopril B: Placebo	8.0% 4.7%	5.0% 4.2%	NR	NR	NR	NR
Rutherford (SAVE) 1994	A: Captopril B: Placebo	NR	6% NR	NR	NR	NR	6% (68/1115) 3% (39/1116)
Shen 1996	A: Captopril B: Placebo	NR	NR	NR	NR	NR	NR
Trials of other ACEIs vs. placebo							
Swedberg (CONSENSUS II) 1992	A: Enalapril B: Placebo	25% 10%	NR	NR	2.4% 1.0%	18% 12%	10% (296/3044) 4.5% (138/3046)
Borghi (FAMIS) 1998	A: Fosinopril B: Placebo	10% 10%	6% 5%	NR	8% 6%	NR	NR
GISSI-3 1994	A: Lisinopril B: Placebo (open)	9% 4%	NR	NR	2.4% 1.1%	Not clear	Not clear
AIRE 1993	A: Ramipril B: Placebo	4% 2%			1.5% 1.2%	35% 32%	13% (126/1004) 7% (68/982)
Ambrosioni (SMILE) 1995	A: Zofenopril B: Placebo	17% 9%	NR	NR	NR	8.6% 6.8%	NR

NR = not reported

Evidence Table 13. Adverse effects reported in head-to-head trials of ACE inhibitors for heart failure

Author Year Country	N	Comparison	Overall Withdrawals	Withdrawals Due to Adverse Effects	Hypotension	Withdrawals due to Hypotension
Acanfora 1997	121	Quinapril 10-20 mg once daily Captopril 12.5-25 mg BID	0% Quinapril 3% Captopril	0% Quinapril 3% Captopril	Not reported	Not reported
Bach 1992	287	Lisinopril 5 -20 mg once daily Captopril 12.5-50 mg BID	12% overall	6% Lisinopril 5% Captopril	Not reported	Not reported
Beynon 1997	61	Captopril 6.25-50 mg BID Quinapril 2.5-20 mg BID	48% Captopril 37% Quinapril	39% Captopril 27% Quinapril	16% Captopril, 17% Quinapril 1st dose hypotension	0% captopril 3% quinapril withdrew due to 1st dose hypotension
Bulpitt	269	Cilazapril 1 mg-2.5 mg once daily Captopril 25 mg TID-50 mg TID	18% overall	Not reported	Not reported	Not reported
Cilazapril-Captopril Study Group	329	Cilazapril 1 mg-2.5 mg once daily Captopril 25 mg TID-50 mg TID	22% Cilazapril 25% Captopril	5.4% Cilazapril 13.0% Captopril	Overall not reported; 0 cilazapril vs 2 captopril experience first-dose hypotension not leading to withdrawal.	Not reported

Evidence Table 13. Adverse effects reported in head-to-head trials of ACE inhibitors for heart failure

Author Year Country	N	Comparison	Overall Withdrawals	Withdrawals Due to Adverse Effects	Hypotension	Withdrawals due to Hypotension
de Graeff 1989	13	Ramipril 5-10 mg BID Captopril 12.5-50 mg TID	33% Captopril 14% Ramipril	14% Captopril 20% Ramipril	Captopril: 20% tolerated only 12.5 mg BID, Ramipril: 29% tolerated only 5 mg due to hypotension 29% Ramipril and 20% Captopril developed symptomatic hypotension (not serious enough to withdraw)	0
Dirksen 1991	40	Enalapril 10-20 mg once daily Captopril 12.5-25 mg TID	Not Clear	11% Enalapril 19% Captopril	0	0
Gavazzi 1994	146	Quinapril 10-20 mg once daily Captopril 25-50 mg BID	11% Captopril 11% Quinapril	7% Quinapril 9% Captopril	4% Captopril, 3% Quinapril had hypotension. 1% captopril, 3% quinapril had 1st dose or orthostatic hypotension. At week 4 increase in dose, 4% captopril, 1% quinapril had hypotension or orthostatic hypotension.	1% captopril withdrew at week 4 after hypotension due to dose increase.
Giles 1988, 1989	65	Lisinopril 5-20 mg once daily Captopril 12.5-50 mg TID	Not reported	2% Lisinopril 2% Captopril	0% lisinopril, 2% captopril hypotension. Symptomatic hypotension in 2% of captopril Subgroup of patients over age 65: 0% lisinopril and 4% captopril had serious hypotension	2% lisinopril discontinued due to mild, nonserious hypotension.

Evidence Table 13. Adverse effects reported in head-to-head trials of ACE inhibitors for heart failure

Author Year Country	N	Comparison	Overall Withdrawals	Withdrawals Due to Adverse Effects	Hypotension	Withdrawals due to Hypotension
Haffner 1995	80	Captopril 12.5 mg BID Enalpril 2.5 mg BID	24 patients withdrew *Total events:* 13 Captopril 14 Enalapril	9 events Captopril 10 events Enalapril	Not reported	0% captopril and 10% enalapril withdrew due to symptomatic hypotension.
Morisco 1997	251	Lisinopril 5-20 mg once daily Captopril 12.5-25 mg BID	16% Lisinopril 13% Captopril	4% Lisinopril 6% Captopril	Not reported	1% captopril, 2% lisinopril withdrew due to hypotension.
Packer 1986	42	Captopril 50 mg TID Enalapril 20 mg BID	0	None	0% captopril, 10% enalapril had 1st dose symptomatic hypotension. 5% enalapril serious hypotension after 6 weeks of treatment.	0
Zannad 1992	278	Lisinopril 5-10 mg once daily Enalapril 5-10 mg once daily	10% Lisinopril 11% Enalapril	9% Lisinopril 6% Enalapril	Not reported	1 lisinopril, 2 enalapril
Zannad 1998	254	Fosinopril 5-20 mg once daily Enalapril 5-20 mg once daily	37% Fosinopril 36% Enalapril	3% Fosinopril 3% Enalapril	All hypotension: 4.9% fosinopril, 4.5% enalapril Symptomatic orthostatic hypotension: 1.6% fosinopril, 7.6% enalapril (p<0.05)	Not reported
Zebrah Study Group (Adgey) 1993	251	Lisinopril 5-20 mg once daily Enalapril 5-20 mg once daily	24% Lisinopril 31% Enalapril	20% Lisinopril 21% Enalapril	1st dose hypotension: 0% lisinopril, 1% enalapril. Hypotension, 2% lisinopril, 1% enalapril	Not reported

Appendix A. Search strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2003>
Search Strategy:

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1 quinapril.mp. (194)
2 benazepril.mp. (133)
3 moexipril.mp. (26)
4 captopril.mp. (1808)
5 enalapril.mp. (1834)
6 lisinopril.mp. (553)
7 ramipril.mp. (343)
8 fosinopril.mp. (122)
9 perindopril.mp. (269)
10 trandolapril.mp. (137)
11 cilazapril.mp. (210)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (4961)
13 congestive heart failure.mp. or exp Heart Failure, Congestive/ (3191)
14 Hypertension/ or high blood pressure.mp. (8790)
15 diabetes mellitus.mp. or exp Diabetes Mellitus/ (7198)
16 myocardial infarct$.mp. or exp Myocardial Infarction/ (7832)
17 exp kidney diseases/ or nephropath$.mp. (4454)
18 13 or 14 or 15 or 16 or 17 (28856)
19 12 and 18 (3233)
20 limit 19 to yr=2000-2003 (483)
21 from 20 keep 1-483 (483)

Database: Ovid MEDLINE(R) <1996 to February Week 2 2004>
Search Strategy:

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1 quinapril.mp. (301)
2 benazepril.mp. (164)
3 moexipril.mp. (31)
4 captopril.mp. (2504)
5 enalapril.mp. (1966)
6 lisinopril.mp. (787)
7 ramipril.mp. (734)
8 fosinopril.mp. (212)
9 perindopril.mp. (510)
10 trandolapril.mp. (270)
11 cilazapril.mp. (181)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (6814)
13 congestive heart failure.mp. or exp Heart Failure, Congestive/ (20810)
14 Hypertension/ or high blood pressure.mp. (33566)

15 diabetes mellitus.mp. or exp Diabetes Mellitus/ (63085)
16 myocardial infarct$.mp. or exp Myocardial Infarction/ (35495)
17 exp kidney diseases/ or nephropath$.mp. (67585)
18 13 or 14 or 15 or 16 or 17 (198734)
19 12 and 18 (4369)
20 limit 19 to (controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (1350)
21 exp Randomized Controlled Trials/ or rct.mp. (22829)
22 systematic review$.mp. (4504)
23 21 or 22 (25921)
24 19 and 23 (233)
25 20 or 24 (1550)
26 limit 25 to (human and english language) (1353)
27 limit 26 to (adult <19 to 44 years> or middle age <45 to 64 years> or "all aged <65 and over>" or "aged <80 and over>") (1149)
28 (200304$ or 200305$ or 200306$ or 200307$ or 200308$ or 200309$ or 20031$ or 2004$).ed. (471964)
29 27 and 28 (122)
30 from 29 keep 1-122 (122)

Database: Ovid MEDLINE(R) <1996 to February Week 3 2004>
Search Strategy:
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1 quinapril.mp. (303)
2 benazepril.mp. (164)
3 moexipril.mp. (31)
4 captopril.mp. (2505)
5 enalapril.mp. (1970)
6 lisinopril.mp. (788)
7 ramipril.mp. (736)
8 fosinopril.mp. (212)
9 perindopril.mp. (512)
10 trandolapril.mp. (272)
11 cilazapril.mp. (181)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (6828)
13 congestive heart failure.mp. or exp Heart Failure, Congestive/ (20853)
14 Hypertension/ or high blood pressure.mp. (33636)
15 diabetes mellitus.mp. or exp Diabetes Mellitus/ (63241)
16 myocardial infarct$.mp. or exp Myocardial Infarction/ (35543)
17 exp kidney diseases/ or nephropath$.mp. (67709)
18 13 or 14 or 15 or 16 or 17 (199134)
19 12 and 18 (4380)
20 limit 19 to (controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (1353)
21 exp Randomized Controlled Trials/ or rct.mp. (22905)

22 systematic review$.mp. (4523)
23 21 or 22 (26010)
24 19 and 23 (233)
25 20 or 24 (1553)
26 limit 25 to (human and english language) (1356)
27 limit 26 to (adult <19 to 44 years> or middle age <45 to 64 years> or "all aged <65 and over>" or "aged <80 and over>") (1152)
28 limit 27 to latest update (3)
29 from 28 keep 1-3 (3)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <March 1, 2004>
Search Strategy:
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1 quinapril.mp. (20)
2 benazepril.mp. (15)
3 moexipril.mp. (2)
4 captopril.mp. (97)
5 enalapril.mp. (102)
6 lisinopril.mp. (51)
7 ramipril.mp. (45)
8 fosinopril.mp. (8)
9 perindopril.mp. (29)
10 trandolapril.mp. (13)
11 cilazapril.mp. [mp=title, abstract] (4)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (343)
13 (congestive heart failure or chf).mp. (624)
14 (Hypertens$ or high blood pressure).mp. (4096)
15 diabetes mellitus.mp. (1451)
16 (myocardial infarct$ or heart attack$).mp. (2094)
17 nephropath$.mp. (680)
18 13 or 14 or 15 or 16 or 17 (8075)
19 12 and 18 (188)
20 from 19 keep 1-188 (188)

Database: EMBASE Drugs & Pharmacology <1991 to 1st Quarter 2004>
Search Strategy:
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1 quinapril.mp. (1398)
2 benazepril.mp. (870)
3 moexipril.mp. (169)
4 captopril.mp. (11583)
5 enalapril.mp. (8437)
6 lisinopril.mp. (3985)

7 ramipril.mp. (2712)
8 fosinopril.mp. (1163)
9 perindopril.mp. (1545)
10 trandolapril.mp. (951)
11 cilazapril.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (996)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (22687)
13 congestive heart failure.mp. or exp Congestive Heart Failure/ (10320)
14 Hypertension/ or high blood pressure.mp. (47700)
15 diabetes mellitus.mp. or exp Diabetes Mellitus/ (61019)
16 myocardial infarct$.mp. or exp Myocardial Infarction/ (33984)
17 exp kidney diseases/ or nephropath$.mp. (77814)
18 13 or 14 or 15 or 16 or 17 (199341)
19 12 and 18 (13642)
20 exp Randomized Controlled Trials/ or randomized controlled trial$.mp. or rct.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (63582)
21 systematic review$.mp. (1478)
22 practice guideline.mp. or exp Practice Guideline/ (29496)
23 meta-analysis.mp. or exp meta analysis/ (12560)
24 multicenter study.mp. or exp multicenter study/ (21894)
25 controlled clinical trial$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (3540)
26 21 or 22 or 23 or 24 or 25 (65036)
27 19 and 26 (1471)
28 limit 27 to (human and english language) (1283)
29 limit 28 to (adult <18 to 64 years> or aged <65+ years>) (576)
30 ("200300" or "200401").em. (171353)
31 29 and 30 (38)
32 from 31 keep 1-38 (38)

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

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

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

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

For Controlled Trials:

Assessment of Internal Validity

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

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or weekdays
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

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

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

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

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

9. Did the study maintain comparable groups?

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

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

Assessment of External Validity (Generalizability)

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

2. How many patients were recruited?

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

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

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

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

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

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

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

3. Were the events investigated specified and defined?

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

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

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

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

Assessment of External Validity

1. Was the description of the population adequate?

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

3. How many patients were recruited?

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

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

Systematic Reviews:

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

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making,

i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

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

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

3. Is the validity of included studies adequately assessed?

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

4. Is sufficient detail of the individual studies presented?

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

5. Are the primary studies summarized appropriately?

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

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