
Oregon Health Resources Commission



Angiotensin-Converting Enzyme Inhibitors (ACEIs)

Subcommittee Report

Update #2, July 2005

This report is an update of the initial
ACE Subcommittee Report of November 2003.
All revisions are highlighted.

Produced by:
Health Resources Commission
Kathleen Weaver, MD, Director
Office for Health Policy & Research
255 Capitol Street NE
Salem, OR 97310

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Overview

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

In the winter of 2003 the Oregon Health Resources Commission (HRC) appointed a subcommittee to perform an evidence-based review of the use of Angiotensin-Converting Enzyme Inhibitors (ACEIs) drugs. Members of the subcommittee consisted of physicians, pharmacists, and a consumer advocate. The subcommittee had three meetings. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities.

Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC draft report, "*Drug Class Review on Angiotensin Converting Enzyme Inhibitors*" was completed the week of September 3, 2003, circulated to subcommittee members and posted on the web. The subcommittee met on September 26, 2003 to review the document and additional evidence. Another meeting was scheduled to give an updated report that included a new study that had just been released. The subcommittee met on October 13, 2002 and by consensus agreed to adopt the amended EPC report. Time was allotted for public comment, questions and testimony. The subcommittee's final meeting was held on November 12, 2003 to review the draft subcommittee report. All available sources of information including the EPC report, information submitted by pharmaceutical manufacturers, and public testimony were considered. The conclusions drawn by the ACEIs Subcommittee comprise the body of this report.

In April 2004 the HRC appointed a Standing Update Committee to perform an evidence-based review of the November 2003 *Angiotensin-Converting Enzyme Inhibitors (ACE-Is) Subcommittee Report* for new information or changes in FDA package inserts. Members of the Standing Update Committee consisted of one HRC member, one OSU pharmacist, one HRC Director, one EPC member, two previous MDs from subcommittees and one pharmacist from subcommittees. Kathy Crispell, MD, a Cardiologist, was also consulted.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Standing Update Committee or the Health Resources Commission. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the Health Resources Commission in providing recommendations to the Department of Human Services. This report is the **second** update of the initial November 2003 Subcommittee Report. All revisions are highlighted.

The Standing Update Committee of the Health Resources Commission, working together with the EPC and the Center for Evidence-based Policy, will monitor medical evidence for new developments in this drug class. Within a year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. The ACEIs report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, have the Standing Update Committee revise the report with minor changes that do not change the Conclusions, or reconvene the ACEIs Subcommittee to revise the report with major changes.

The full OHSU Evidence-based Practice Center's draft report, *Drug Class Review on ACE-Is Drugs Updated Final Report #2, June 2005*, is available on the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website: www.oregonrx.org. Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: www.ohpr.state.or.us/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml. You may request more information including copies of the draft report, minutes and tapes of subcommittee meetings, from:

Kathleen Weaver, MD
Director, Health Resources Commission
Office for Oregon Health Policy & Research
255 Capitol St. NE, 5th Floor
Salem, Oregon 97310
Phone: 503-378-2422 ext. 406
Fax: 503-378-5511
Email: Kathy.Weaver@state.or.us

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

John Santa, MD
Assistant Director for Health Projects
OHSU-Center for Evidence-based Policy
2611 SW 3rd Avenue, MQ280
Portland, OR 97201-4950
Phone: 503-494-3094 Email: santaj@ohsu.edu

There will be a charge for copying and handling in providing documents both from the OHPR and from the Center.

Critical Policy:

- *Senate Bill 819*
 - “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”
- *Health Resources Commission*
 - “Clinical outcomes are the most important indicators of comparative effectiveness”;
 - “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Definition of Angiotensin Converting Enzyme Inhibitors (ACEIs)

ACEIs block the activation of the renin-aldosterone system, an important mediator of blood pressure. In addition to their effects on blood pressure, recent evidence suggests that some ACEIs have benefits independent of blood pressure lowering such as ventricular remodeling following myocardial infarction or 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 that are post-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.

¹ Ryan TJ, Antman EM, Brooks NH, et al. ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction: Executive Summary and Recommendations. *Circulation* 2001; 100(9):1016-1030

² Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult. American College of Cardiology Website 2001; http://www.acc.org/clinical/guidelines/failure/hf_index.htm

³ Smith SC, Jr., Blair SH, Bonow RO, et al. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update. *Circulation* 2001;104:1577-1579

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) recommended thiazide diuretics as the first-line option for patients with hypertension without compelling indications for another agent, although they note that most patients will eventually need two drugs to control hypertension.⁴ ACEIs are recommended as one of several acceptable first-line options for patients who have hypertension in combination with compelling indications such as: heart failure, diabetes, chronic kidney disease, high cardiovascular risk, a history of recent myocardial infarction, or a history of stroke.

This review covers the ten ACEIs currently marketed in the United States:

■ ***ACE Drugs:***

<u>Generic</u>	<u>Brand(s)</u>
– Benazepril	Lotensin
– Captopril	Capoten
– Enalapril	Vasotec
– Fosinopril	Monopril
– Lisinopril	Prinivil, Zestril
– Moexipril	Univasc
– Perindopril	Aceon
– Quinapril	Accupril
– Ramipril	Altace
– Trandolapril	Mavik

Quality of the Evidence

The subcommittee utilized the EPCs ratings of good, fair or poor to weigh the body of evidence for each key question. The subcommittee took into account the number of studies, the total number of patients in each study, the length of the study periods and the end-point(s) of the studies. Statistical significance was a prime consideration. Because of the many large, randomized studies of these agents, ACEIs are well suited to an evidence-based approach to formulary decision-making, but ACEIs must have demonstrated efficacy in controlled trials. While all of these agents have demonstrated efficacy in the management of hypertension, some have demonstrated additional benefits independent of blood pressure lowering such as end-organ protection (See Table 1.)

⁴ Chobanian AV, Bakris GL, African-Americans HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. JAMA 2003;289:2560-2572

Inclusion Criteria:

■ *Scope*

- Patients and indications:
 - Heart failure (HF)
 - Hypertension. (Blood pressure over 140/90 mm Hg)
 - High cardiovascular risk
 - Recent myocardial infarction
 - Diabetic nephropathy
 - Non-diabetic nephropathy

■ *Interventions*

- Drug may be started in the hospital, emergency room, or in the ambulatory setting.
- Studies conducted entirely in the inpatient setting are excluded.

■ *Efficacy Measures- the main efficacy measures depend on the indications:*

- Hypertension
 - All cause mortality and cardiovascular (CV) mortality
 - CV events: Stroke, MI, development of HF
 - End-stage renal disease (ESRD) or need for dialysis or transplantation
 - Clinically significant, permanent increase in serum creatinine or decrease in creatinine clearance
 - **NOT:** Angina, unstable angina, angioplasty, coronary artery bypass graft (CABG), transient ischemic attack (TIA)
- Recent Myocardial Infarction (MI)
 - All cause mortality and CV mortality
 - Onset of HF
- HF
 - All cause mortality and CV mortality
 - Symptomatic improvement. Measures may include but not be limited to HF class, SF36 results, and visual analog scales
 - Hospitalization for HF exacerbation (provided that those making the decision about hospitalization are masked to treatment assignment)
 - **NOT:** Clinician judgment of improvement, subjective statements about activity tolerance)

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- High Cardiovascular Risk
 - All-cause mortality and CV disease mortality
 - CV Events
 - Diabetic Nephropathy
 - ESRD or need for dialysis or transplantation
 - Clinically significant, permanent increase in serum creatinine or decrease in creatinine clearance
 - Non-diabetic Nephropathy
 - ESRD or need for dialysis or transplantation
 - Clinically significant, permanent increase in serum creatinine or decrease in creatinine clearance
- *Safety and Adverse Effects*
- Withdrawals
 - Withdrawals due to adverse effects
 - Specific adverse effects or withdrawals due to specific adverse events, including:
 - Acute renal failure
 - Cough
 - Hyperkalemia
 - Symptomatic hypotension
 - Angioedema

Exclusions:

- No original data: Study does not contain original data (e.g., review, editorial, letter with no original data)
- Studies of combinations of interventions as initial therapy

Key Questions:

1. For hypertension, HF, recent MI, high cardiovascular risk, diabetic or non-diabetic nephropathy do ACEIs² differ in efficacy?
2. For hypertension, HF, recent MI, high cardiovascular risk, diabetic or non-diabetic nephropathy do ACEIs differ in safety or adverse effects?
3. Are there subgroups of patients based on race, ethnicity, gender, use of other medications, or co-morbidities, for which ACEIs differ in effectiveness or adverse effects?

Inclusion Criteria for Key Questions

1. Studies of adult patients with hypertension, HF, recent MI, high cardiovascular risk, diabetic nephropathy, or non-diabetic nephropathy.
2. Timing of the intervention: drug may be started in the hospital, emergency room, or in the ambulatory setting. Studies conducted entirely in the inpatient setting are excluded.
3. For effectiveness, study is a randomized controlled trial. Primary consideration will be given to direct evidence from randomized trials reporting the effect of ACEIs on mortality and other major endpoints.
4. For adverse effects, study is a controlled clinical trial or observational study, of at least 6 months duration. Drug-drug interaction studies of shorter duration will be included.

New Findings

- Since April 2004 there have been no new ACEIs added in the USA.
- The Center for Evidence-Based Policy solicited input from the pharmaceutical industry and included them in their report if they met the EPC's criteria for inclusion.
- FDA information: New **WARNINGS** for intestinal angioedema have been reported in patients treated with ACEIs. Also hepatic failure and jaundice have been added to the **ADVERSE REACTIONS/Gastrointestinal** subsection. Under **Geriatric Use:** Clinical studies of ACEIs in patients with hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.
- Using the same search strategy that was used in the original ACEI report, the EPC found 770 new citations of which 17 met inclusion criteria: 2 active controlled and 1 placebo-controlled trials, one new systematic review, and 13 observational studies.

Amended Summary of Results

Key Question 1a. For patients with hypertension do ACEIs differ in efficacy?

Although a recent comprehensive meta-analysis identified 9 controlled trials reporting major cardiovascular disease end points and all-cause mortality involving various ACEIs, none of the trials were designed to compare one ACEI to another. 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. No outcomes were assessed in head-to-head trials.

One good long-term (24 week) quality-of-life study reported that captopril was better than enalapril, although blood pressure lowering was equivalent. A shorter (8 week) good quality head-to-head trial found no difference in efficacy for reducing blood pressure or quality of life among hypertensive men randomized to captopril, enalapril, or beta-blockers.

For patients with hypertension with compelling indications such as diabetes or a history of stroke, the ACEIs were better than a calcium channel blocker and equivalent to a beta-blocker, for reducing the incidence of MI, or the combined endpoint of MI, stroke or hospitalization for angina. Yet none of these **studies** compared ACEIs head-to-head for their treatment of compelling indications associated with hypertension.

Post-hoc subanalysis from **SOLVD** (enalapril), **HOPE** (ramipril), **ALLHAT** (lisinopril), and **CAAPP** (captopril) provide strong evidence that ACEIs delay or prevent the development of diabetes. The **DREAM** (Diabetes REduction Approaches with ramipril and rosiglitazone Medications) trial currently in progress, will evaluate the effectiveness of ramipril and rosiglitazone for the prevention of diabetes in over 5,000 patients with impaired glucose tolerance. This is the first study of an ACEI prospectively designed to evaluate the development of diabetes as a primary endpoint.⁵

The Standing Update Committee agrees by consensus that in patients with hypertension there are no data to suggest that one ACEI is superior to another.

Key Question 1b. For patients with high cardiovascular risk factors do ACEIs differ in efficacy?

Eleven fair trials have enrolled patients who have coronary artery disease or who have risk factors for cardiovascular disease, but not hypertension. The **HOPE** trial (N=9,287) showed that ramipril reduced major cardiovascular events (NNT=26.7) and all-cause mortality (NNT=56) in all groups except for patients who had no history of cardiovascular disease. Ramipril also reduced the rate of the composite heart failure endpoint of heart failure death, heart failure requiring hospitalization, heart failure requiring an ACEI, or any reported heart failure. (RR 0.77; 95% CI 0.68, 0.87).⁶ The recently released very large (n=12,218) **EUROPA** trial enrolling patients with stable coronary artery disease, showed that perindopril reduced combined cardiovascular events (NNT=50), but failed to significantly reduce all-cause mortality. However the **EUROPA** trial had a 4-week run-in

⁵ Gerstein HC. Rationale, design and recruitment characteristics of a large, simple international trial of diabetes prevention: The DREAM trial. *Diabetologica* 2004;47(9):1519-1527

⁶ Arnold JMO, Yusuf S, Young J, et al. Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (**HOPE**) study. *Circulation*. 2003;107(9):1284-1290.

period during which time 75 patients who had taken perindopril, had major clinical events. This would change the NNT=125 to prevent one cardiovascular event in four years. **QUIET**, a post-angiographic study following patients for 2 years, was too low-powered to detect a difference in cardiovascular events. In the trial **PART2**, ramipril significantly lowered major cardiovascular events (NNT=45), but only had a trend towards reduced all-cause mortality. In **SCAT** a combined trial of Simvastatin/Enalapril, the major cardiovascular events were reduced, but the small (229) number of patients prevented assessment of all-cause mortality. In addition, the **PROGRESS** trial enrolled normotensive patients who had a previous stroke and found that perindopril alone without diuretics, did not reduce the risk of recurrent stroke.

PEACE was a large, good quality trial of trandolapril versus placebo in patients with coronary disease and normal LV function. There was no difference between trandolapril and placebo in the incidence of CV events or in all-cause mortality after 4.8 years.

DIABHYCAR, a large (4,912) study of patients with diabetic nephropathy, is discussed here because its primary outcome measures were mortality and cardiovascular disease. Patients with type 2 diabetes and 56% with hypertension were randomized to **low** dose ramipril (1.25mg) or placebo. After 3-6 years ramipril had no effect on cardiovascular and renal outcomes.

The Standing Update Committee agrees by consensus that in patients with high cardiovascular risk:

- *Ramipril, perindopril, and enalapril have been shown to reduce major cardiovascular events in patients with coronary artery disease.*
- *Ramipril is the only ACEI shown to reduce all-cause mortality.*

Key Question 1c. For patients with recent myocardial infarction do ACEIs differ in efficacy?

Head-to-head trials. In patients who have had a MI, ACEIs are given to prevent the development or progression of heart failure and to reduce mortality irrespective of the presence of heart failure. All-cause mortality and other outcomes were evaluated in two fair quality head-to-head trials, but with low numbers (n=225 and n=212) of enrolled patients 24-72 hours after onset of symptoms of MI. Heart failure was not a requirement for entry. The first trial measured mortality as a secondary endpoint and found a significant difference in mortality after 1 year (13% vs. 3%) comparing captopril vs. enalapril. However, in the second study in which mortality was a primary endpoint, there were no

significant differences for mortality or revascularization rates for captopril vs. perindopril at 6 months.

Placebo-controlled trials. Two fair-quality systematic reviews of 18 trials assessed the effects of ACEIs on mortality following MI. 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 MI could be seen from large placebo-controlled trials. The NNT across studies are not comparable because the duration of follow-up 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 two systematic reviews were not designed to assess comparative efficacy.

Captopril, lisinopril, ramipril, and trandolapril reduced mortality and heart failure in good quality, placebo-controlled trials. The picture with enalapril is confusing in that one large, good-quality placebo-controlled trial actually showed a trend towards increased mortality, but significantly reduced heart failure. In a smaller placebo-controlled trial, fosinopril also created a trend towards increased mortality, yet decreased heart failure.

The Standing Update Committee agrees by consensus that in patients with recent MI:

- *In good quality placebo controlled trials, captopril, lisinopril, ramipril and trandolapril all reduce mortality and heart failure.*
- *Enalapril was superior to captopril for reducing all-cause mortality.*
- *There were no significant differences in mortality reduction or revascularization rates between captopril vs. perindopril after recent MI.*

Key Question 1d. For patients with HF do ACEIs differ in efficacy?

Head-to-head

There was fair evidence from head-to-head trials of captopril (10), enalapril (6), fosinopril (1), lisinopril (5), quinapril (3), and ramipril (1); but none from benazepril, trandolapril, moexapril, or perindopril in patients with HF. Most trials enrolled patients with New York Heart Association (NYHA) functional class II or III HF; but two trials enrolled only more severe patients with class III to IV HF or left ventricular ejection fraction (LVEF) less than 30%.

Only one head-to-head trial reporting mortality as a primary outcome showed no difference in total mortality between fosinopril vs. enalapril. The combined endpoint of total hospitalization plus death was significantly smaller ($p=0.03$) in the fosinopril group, but the dosing schedule of enalapril (5 to 20 mg once daily) was not optimal. The best evidence about the effectiveness of ACEIs on mortality in patients with heart failure comes from five large placebo controlled trials: SAVE(captopril), CONSENSUS(enalapril), SOLVD(enalapril), AIRE(ramipril), and TRACE(trandolapril).

There was good quality evidence for functional outcomes. In 11 out of 15 trials that used change in NYHA functional class as an outcome measure, the ACEIs improved NYHA class regardless of which ACEI patients were taking. In fair quality head-to-head trials there was no evidence that one ACEI was superior to another for improvement in NYHA class or exercise tolerance and duration.

Placebo-controlled trials

One fair quality meta-analysis of 32 placebo-controlled trials showed no difference in mortality or mortality plus hospitalization among benazapril, captopril, enalapril, lisinopril, perindopril, quinapril and ramipril. There was a significant reduction in all-cause mortality in patients allocated to a treatment group, but no heterogeneity of effect among the ACEIs. There was no difference among the ACEIs on the combined endpoint of total mortality or hospitalization in 30 trials that provided this information. Overall results were similar for cause-specific mortality, but comparisons among ACEIs were not made for these sub analyses.

There were no placebo-controlled heart failure trials for fosinopril, moexipril, or trandolapril.

The Standing Update Committee agrees by consensus that for patients with HF:

- *Benazapril, captopril, enalapril, lisinopril, perindopril, quinapril and ramipril have been shown to reduce morbidity and mortality from heart failure.*
- *ACEIs improve NYHA functional class or exercise tolerance, but there are no differences among captopril, enalapril, fosinopril, lisinopril, quinapril, or ramipril.*
- *Head-to-head and placebo controlled trials for reduction in morbidity or mortality are not available for moexapril and trandolapril.*

Key Question 1e. For patients with diabetic nephropathy, do ACE Inhibitors differ in efficacy?

Although there were over 300 publications that addressed renal disease in diabetes, there were no head-to-head trials of ACEIs in patients with diabetic nephropathy. ACEIs reduce or eliminate microalbuminuria, an early sign of renal damage in diabetics (and non-diabetics). They have also been used in patients with frank proteinuria (>3 gm/d) and/or in patients with decreased renal function.

Type 1 Diabetes

The most compelling reference, the 1993 Collaborative Study Group trial, was the first study to demonstrate that an ACEI reduced the incidence of advanced renal failure. These were long-standing (average 22 years), poorly controlled (average hemoglobin A1c = 11.7%), multiply co-morbid (75% had hypertension) patients followed for 3 years with a dramatic improvement of creatinine doubling, death, dialysis, or transplant (NNT=10, p=0.007) from captopril.

Subsequently, two large trials, the European Microalbuminuria Captopril Study Group (**EMCSG**) and the North American Study Groups (**NAMSG**), have demonstrated that in Type 1 diabetes with microalbuminuria and without hypertension, captopril prevented the onset of clinical proteinuria and hypertension. In the **NSMAG** trial, creatinine clearance remained stable, whereas the placebo group decreased by 10 ml/min over two years. However, neither study demonstrated an effect on the risk of developing ESRD. Lisinopril and perindopril also reduce proteinuria, but have not been shown to prevent the development of renal failure in Type 1 diabetics.

Type 2 Diabetes

While ACEIs reduce albuminuria in normotensive type 2 diabetics with microalbuminuria, they have not been shown to prevent the development of ESRD in this group.

Diabetes Prevention

Although not involving a key question for the EPC, a post-hoc analysis from Studies of Left Ventricular Dysfunction (**SOLVD**) and from Heart Outcomes Prevention Evaluation (**HOPE**) provided strong evidence that enalapril and ramipril delay or prevent the development of diabetes.

The Standing Update Committee agrees by consensus that in patients with diabetic nephropathy:

- *Captopril reduces ESRD and death in patients with poorly controlled, longstanding Type 1 diabetes.*
- *Benazepril significantly reduces the risk of developing ESRD or a doubling of serum creatinine in Type 1 and 2 diabetics.*

-
- *Captopril prevents the onset of proteinuria, hypertension, and worsening renal function in Type I diabetics with microalbuminuria.*

Key Question 1f. For patients with non-diabetic nephropathy do ACE Inhibitors differ in efficacy?

In a large trial of patients with renal insufficiency from various causes, benazepril reduced the risk of developing ESRD or a doubling of the creatinine by 50%. Only 21% of the patients had diabetic nephropathy, but the effect was stronger in this subgroup than in the sample as a whole.

The Standing Update Committee agrees by consensus that in patients with non-diabetic nephropathy, benazepril significantly reduces the risk of developing ESRD or a doubling of serum creatinine.

Key Question 2 For general indications such as patients with hypertension, HF, or MI, do ACEIs differ in safety or adverse effects?

Adverse effects of ACEIs include hypotension, dry cough, angioedema, hyperkalemia, rash, hepatotoxicity, dysgeusia (i.e., distortions of taste), neutropenia, and acute renal impairment. Angioedema, although usually mild, can be severe with compromise of the airway requiring intravenous antihistamines or intubation. Dysgeusia and neutropenia were seen primarily with the use of high doses of captopril >100 mg/day.

Head-to-head trials

Twenty-four fair head-to-head trials compared the rates of adverse events from ACEIs available in the US. Nine of these concerned patients with hypertension, two concerned post-MI patients, and 13 concerned patients with heart failure. Adverse event assessment quality was generally worse than quality for assessing clinical efficacy.

In patients with hypertension there were no important differences in quality of life, rates of cough, angioedema, hyperkalemia, or acute renal impairment. Following MI, adverse events were not specified and potential confounders were not evaluated. Neither study found significant differences among ACEIs for overall withdrawals, cough, or symptomatic hypotension. In the 15 head-to-head

trials concerning heart failure, the percentage of patients who withdrew due to adverse events ranged from 0-39%, but did not differ between ACEIs in any trial. Five trials reported the number of deaths that occurred during the treatment period, but found to find a significant difference between groups.

Placebo-controlled trials

In 12 large placebo-controlled trials of ACEIs post-MI, adverse event assessment was only fair. Trials did not adequately report adverse event assessment techniques or pre-define adverse events. The most consistently reported adverse event was hypotension, but again, definition of “significant” hypotension varied widely between studies. For hypotension, no clear pattern of one ACEI being superior to another was noted from these trials. Other adverse events such as cough, angioedema, significant renal failure, and withdrawal due to adverse events were inconsistently reported, and no reliable conclusions could be drawn from the data.

The Standing Update Committee agrees by consensus that in patients with hypertension, HF, or MI there is no evidence that any ACEI is associated with a lower risk of serious complications than any other ACEI.

Key Question 3.

Are there subgroups of patients based on race, ethnicity, gender, use of other medications, or co-morbidities, for which ACEIs differ in effectiveness or adverse effects?

No data suggest that one ACEI is better than others for demographic subgroups based on age, race, or gender although the recommended initial dose of trandolapril is higher for African-Americans than non-African-American patients. A meta-analysis of the effectiveness of ACEIs in heart failure made 3 comparisons: African-Americans vs. whites, men vs. women, and diabetics vs. nondiabetics.⁷ In diabetes and in African-Americans, the effect of ACEIs were similar to those in general population. However, women seemed to benefit less than men. ACEIs have more beneficial effects in post-MI patients at higher risk for recurrent cardiovascular events, but no single ACEI has been found to be superior for any of these conditions.

At present, the role of ACEIs in the management of hypertension, post-MI, HF, and kidney disease is the same for African-Americans and non-African-Americans. In head-to-head trials, there are no data to suggest that one ACEI is

⁷ Shekelle PG, Rich MW, Morton SC, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic statuses. A meta-analysis of major clinical trials. *J Am Coll Cardiol* 2003; 41:1529-1538.

superior to another. African-American patients who take ACEIs are at a 2-4 times higher risk of developing angioedema than other Americans. There is currently no evidence that one ACEI is safer than others for African-American patients.

One fair quality head-to-head trial of lisinopril vs. captopril analyzed a subgroup of 65 patients over age 65. There was no difference between treatment groups in change of NYHA class after 12 weeks of treatment.

ACEIs appear to be effective when used in conjunction with nitrates, aspirin, thrombolytics and other agents conventionally used to treat MI, but there are no data regarding comparative efficacy or safety in patients on these medications.

The Standing Update Committee agrees by consensus that:

- *There are no data on how different ACEIs are superior to any other ACEI in women.*
- *There is not conclusive evidence on how different ACE Inhibitors compare in African-Americans.*
- *Evidence from a HF meta-analysis showed no differences among ACEI based on patient age.*

Conclusion

In a series of public meetings with the opportunity for public questions, comment and testimony, the Standing Update Committee of the Health Resources Commission reviewed the medical evidence comparing ACE-Inhibitors. The OHSU EPC's report, "Drug Class Review on ACE-Inhibitor Drugs Updated Final Report #1," which included appropriate information presented in pharmaceutical manufacturer dossiers, was reviewed and public testimony considered.

Using all of these sources of information, the Standing Update Committee arrived at the following conclusions about the comparative effectiveness and safety of ACEI drugs as supported by analysis of the medical literature:

It is the decision of the Standing Update Committee that:

1. In patients with hypertension there are no data to suggest that one ACEI is superior to another.
2. In patients with high cardiovascular risk, ramipril, perindopril, and enalapril have been shown to reduce major cardiovascular events in patients with coronary artery disease, but ramipril is the only ACEI shown to reduce all-cause mortality.
3. In patients with recent MI:
 - ◆ captopril, lisinopril, ramipril, and trandolapril all reduce mortality and heart failure.
 - ◆ enalapril was superior to captopril for reducing all-cause mortality.
 - ◆ there were no significant differences in mortality reduction or revascularization rates between captopril vs. perindopril.
4. In patients with chronic HF benazepril, captopril, enalapril, lisinopril, perindopril, quinapril and ramipril reduce morbidity and mortality from heart failure.
5. In patients with diabetic nephropathy, captopril reduces ESRD and death in patients with poorly controlled, longstanding Type 1 diabetics.
6. In patients with non-diabetic nephropathy, benazepril significantly reduces the risk of developing ESRD or a doubling of serum creatinine.
7. In patients with hypertension, HF, or MI there is no evidence that any ACEI is associated with a lower risk of serious complications than any other ACEI.
8. There are no data on how different ACEIs are superior to any other ACEI in women or African-Americans. Evidence from a HF meta-analysis showed no differences among ACEIs based on patient age.

Walter Shaffer, MD

Chair, Health Resources Commission

Paul Tiffany

Vice Chair, Health Resources Commission

David Labby, MD

*Chair, Standing Update Committee
Health Resources Commission*

Bruce Goldberg, MD

*Administrator
Office for Health Policy & Research*

Kathleen Weaver, MD

*Director, Health Resources Commission
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Dan Kennedy, RPh
Dean Haxby, PharmD
Mark S. Yerby, MD
John W. Saultz, MD
Lynn-Marie Crider
Manny Berman

Subcommittee Members

Dana Selover, MD
David Clark, RPh
Mark Rosenberg, MD
Robert Gluckman, MD
Enid Moore
Christina Heinrich, PharmD

Health Resources Commission

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

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

TABLE 1
SUMMARY OF EVIDENCE ACEIs

DRUG	HTN w/o compelling indications	HTN w/DM	HTN w/STROKE	HIGH CARDIAC RISK	RECENT MI	Heart Failure (HF)	DM NEPHROPATHY	NON-DM NEPHROPATHY
BENAZEPRIL						Reduced Mortality	Reduced ESRD/21% DM	Reduced ESRD/79% Non-DM
CAPTOPRIL	=diuretic, BB	=BB			Reduced Mortality	Reduced Mortality	Reduced ESRD and onset of HTN	
ENALAPRIL	>diuretic >captopril	>CCB		Reduced Major Cardiac Events	>Captopril in small H-to -H, but otherwise inconsistent	Improved functional outcomes; Reduced mortality		
FOSINOPRIL		>CCB			No Mortality Benefit	= enalapril, and NS trend toward lower mortality		
LISINOPRIL	<diuretic				Reduced Mortality	Improved function and Reduced mortality		
MOEXIPRIL								
PERINDOPRIL			= placebo stroke prevention	Reduced Major Cardiac Events		Reduced mortality		
QUINAPRIL				No difference from placebo		Improved Fn outcome reduced mortality		
RAMIPRIL				Reduced all cause mortality and major CV events	Reduced mortality and heart failure	Improved functional outcomes & reduced mortality	Reduced ESRD/death in blacks w/ HT renal	Reduced ESRD/death in blacks w/non-DM renal disease
TRANDOLAPRIL					Reduced mortality and HF			

HTN - Hypertension
DM – Diabetes Mellitus
MI – Myocardial Infarction
HF – Heart Failure

BB – Beta-blocker
ESRD – End Stage Renal Disease
CCB – Calcium Channel Blocker
QOL – Quality of Life

NS – Not Significant
CV - Cardiovascular
Fn – Functional
H-to-H – Head-to-Head