

Drug Class Review on ACE Inhibitors

Update #3: Preliminary Scan Report 4

March 2010

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

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

June 2005 (searches through February 2005)

Date of Last Update Scans

Scan #1: February 2007

Scan #2: February 2008

Scan #3: November 2008

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Questions

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 (ACE) inhibitors differ in effectiveness?
2. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do ACE inhibitors differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one ACE inhibitor is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

ACE Inhibitors
Update #3

Adult patients with any of the following indications:

- Hypertension without compelling indications. This refers to patients with hypertension who do not have any of the following indications:
 - a. a history of coronary heart disease (CHD)
 - b. other cardiovascular diseases (CVD), such as cerebrovascular (carotid) disease, peripheral vascular disease, or a history of stroke
 - c. other risk factors for CAD/CVD, such as diabetes, smoking or hyperlipidemia
 - d. 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, or a combination of other risk factors for CHD/CVD, such as diabetes, 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.

Interventions

- benazepril
- captopril
- cilazapril
- enalapril
- fosinopril
- lisinopril
- moexipril
- quinapril
- ramipril
- perindopril
- trandolapril

Effectiveness outcomes

Effectiveness measures varied according to the clinical condition:

Hypertension

- All-cause and cardiovascular mortality
 - Cardiovascular events (stroke, myocardial infarction, or development of heart failure)
 - 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)
 - Quality-of-life
- (Trials that focused on blood pressure reduction but not on any health outcomes were excluded from the effectiveness review)

High cardiovascular risk

- All-cause and cardiovascular mortality
- Cardiovascular events (stroke, myocardial infarction, or development of heart failure)

Recent myocardial infarction

- All-cause and cardiovascular mortality
- Cardiovascular events (usually, development of heart failure)

Heart failure

- All-cause or cardiovascular mortality
- Symptomatic improvement (heart failure class, functional status, visual analogue scores)
- Hospitalizations for heart failure

Diabetic nephropathy/non-diabetic nephropathy

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

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Specific adverse effects or withdrawals due to specific adverse events, for example, symptomatic hypotension

Study designs

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

METHODS**Literature Search**

To identify relevant citations, we searched Ovid MEDLINE from November 2008 through February Week 3, 2010, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (<http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2010/index-eng.php>) websites for identification of new

drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X1) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 198 citations. Of those, there were 2 new potentially relevant trials (see Appendix A, attached). The characteristics of these trials are shown in Table 1. One was a subgroup analysis of the EUROPA trial, already included in the DERP ACE Inhibitors report.

Table 1. Potentially relevant trials of ACE Inhibitors identified for Update #3 Scan #4

Author, year	Comparison	Population	Main Outcomes	Comment
Bertrand 2009	Perindopril 8 mg vs placebo	Prior MI and/or revascularization	Composite of cardiovascular mortality, MI, and resuscitated cardiac arrest.	Subgroup analysis of EUROPA Trial
Hsia 2008	Trandolapril vs placebo	Stable CAD and preserved left ventricular systolic function	Sudden cardiac death	

Taken together with the 23 trials identified in Preliminary Update Scan #1, 13 trials identified in Scan #2, and 8 trials identified in Scan #3, there are now a total of 46 potentially relevant trials available for this topic.

New Drugs

No new ACE Inhibitors were identified.

New Indications

No new indications were identified.

New Safety Alerts

No new safety alerts were identified.

Appendix A. Abstracts of potentially relevant new trials of ACE Inhibitors

Bertrand, M. E., K. M. Fox, et al. (2009). "Angiotensin-converting enzyme inhibition with perindopril in patients with prior myocardial infarction and/or revascularization: a subgroup analysis of the EUROPA trial." Archives of cardiovascular diseases **102**(2): 89-96.

BACKGROUND: The European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) demonstrated the benefits of perindopril with respect to secondary prevention of cardiovascular risk in patients with stable coronary artery disease. **AIMS:** To describe the clinical effects of perindopril in a subpopulation of patients from EUROPA with a history of myocardial infarction and/or revascularization. **PATIENTS AND METHODS:** Of the 12,218 patients in the EUROPA study, 10,962 had a history of myocardial infarction and/or revascularization. In this EUROPA subpopulation, 7910 patients had a history of myocardial infarction and 6709 had a history of revascularization. Patients were randomized to treatment with perindopril 8mg/day or placebo. The primary endpoint was a composite of cardiovascular mortality, myocardial infarction and resuscitated cardiac arrest. **RESULTS:** After a mean follow-up of 4.2 years, treatment with perindopril 8mg/day was associated with a 22.4% reduction in the primary endpoint compared with placebo ($p < 0.001$) in patients with a history of myocardial infarction. Patients with a history of myocardial revascularization showed a 17.3% reduction in the primary endpoint with perindopril versus placebo ($p < 0.05$). In the combined population of patients with a history of myocardial infarction and/or revascularization, treatment with perindopril produced a 22.4% reduction in the primary endpoint compared with placebo ($p < 0.001$). **CONCLUSIONS:** This study confirms the benefits of a high dose of angiotensin-converting enzyme inhibitor for the secondary prevention of cardiovascular risk among patients with a history of myocardial infarction and/or revascularization.

Hsia, J., K. A. Jablonski, et al. (2008). "Sudden cardiac death in patients with stable coronary artery disease and preserved left ventricular systolic function." American Journal of Cardiology **101**(4): 457-61.

Although sudden cardiac death (SCD) has been extensively studied in patients with coronary artery disease (CAD) and low ejection fraction, prediction of SCD among individuals with preserved left ventricular systolic function is less well understood. We randomized 8,290 patients with stable CAD with preserved left ventricular systolic function to trandolapril or placebo in a secondary coronary prevention trial, and we used Cox proportional hazards models to identify independent baseline predictors of SCD during 4.8 year follow-up (median). Using a risk scoring algorithm based on simple clinical characteristics, we were able to distinguish individuals at higher risk for SCD. Independent determinants of SCD included age ($p < 0.001$), current angina pectoris ($p = 0.002$), ejection fraction $>40\%$ to $<50\%$ (as opposed to $>50\%$) ($p < 0.001$), and diuretic ($p < 0.001$) and digitalis use ($p < 0.001$). Negative predictors included having prior coronary revascularization ($p = 0.01$) and being female ($p = 0.02$) or Caucasian ($p = 0.006$). Trandolapril neither increased nor decreased SCD. Thus, among patients with stable CAD with preserved left ventricular systolic function receiving current standard-of-care including coronary revascularization, clinical characteristics can identify individuals at higher risk for SCD.