Title: Angiotensin-Converting Enzyme (ACE) inhibitors: A Comparative Effectiveness Review

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Context and policy issues:

Cardiovascular disease is the leading cause of death for men and women worldwide. In Canada, cardiovascular disease accounted for 32% (over 72,000) of all deaths in 2004. The continuum of cardiovascular disease begins with risk factors, such as hypertension, and progresses to atherosclerosis and target organ damage, ultimately leading to heart failure or stroke. Angiotensin-converting enzyme (ACE) inhibitors have become vital tools in the medical therapy of hypertension and cardiovascular disease. Evidence from clinical trials has shown that ACE inhibitors have the broadest impact of any drug in cardiovascular medicine, reducing the risk of death, myocardial infarction, stroke, diabetes, and renal impairment. They benefit patients with heart failure or left ventricular dysfunction, post-myocardial infarction, peripheral vascular disease, diabetes, stroke, transient ischaemic attack, or coronary artery disease.

ACE inhibitors block the activation of the renin-angiotensin system (RAS), which is an important mediator of blood pressure and its dysfunction plays a central role in the pathogenesis of many types of cardiovascular disease. The first ACE-inhibitor, captopril, was introduced into the healthcare market in 1981. Since many of the side effects of captopril, such as proteinuria, skin rashes, and altered taste, were attributed to its sulfhydryl group, other ACE inhibitors were developed that replaced this group with a carboxyl group (e.g., enalapril, lisinopril, benazepril, quinapril, ramipril, perindopril, cilazapril, trandolapril) or a phosphoryl group (fosinopril). The presence of the carboxyl group conferred greater lipophilicity, which improved tissue penetration and binding to ACE. Since ACE inhibitors are structurally heterogeneous, each has distinct pharmacokinetic and pharmacodynamic features, such as differences in absorption, protein binding, half-life, and metabolic disposition.

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Many of the therapeutic benefits derived from ACE inhibitors are thought to be “class effects”. Although drugs within a class share main actions, they may have clinically important differences in terms of efficacy and safety. In appropriate doses, all ACE inhibitors lower blood pressure to a similar extent. It has been speculated, however, that all ACE inhibitors are not interchangeable in the treatment of other aspects cardiovascular disease (e.g. congestive heart failure), where effects other than blood pressure normalization are the goal. Comparative clinical effectiveness is best determined by trials that directly compare drugs or dosages head-to-head.

In light of the fact that several ACE inhibitors are currently available in Canada (including benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, and trandolapril), a review of evidence for comparative safety and efficacy is necessary to help guide formulary decisions. This report will review current evidence from head-to-head trials assessing the efficacy of ACE inhibitors for reducing high blood pressure, kidney protection and other outcomes.

Research question:

What is the comparative effectiveness of ACE inhibitors for reducing blood pressure, kidney protection and other outcomes?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and March 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews/health technology assessments and RCTs. This search was supplemented by hand searching the bibliographies of selected papers.

Summary of findings:

Health technology assessments

One health technology assessment, published in 2005 by the Oregon Evidence-based Practice Center, was identified. The purpose of this report was to provide information regarding the comparative effectiveness and safety profiles of different ACE inhibitors. Placebo-controlled randomized controlled trials (RCTs) and head-to-head RCTs were included in the assessment of effectiveness, and RCTs or large, good-quality observational studies were included in the assessment of harms. Included interventions were treatment with benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, perindopril, or trandolapril. Outcomes varied according to the clinical indication. The overall grade of evidence was based on methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; adequate reporting of dropouts; and the use of intention-to-treat analysis. Results from head-to-head trials for the comparative effectiveness of ACE inhibitor treatment and the overall grade of evidence are summarized in Table 1.
Table 1: Summary of evidence for comparative effectiveness of ACE inhibitor treatment from head-to-head RCTs.

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Outcomes</th>
<th>Overall Grade of Evidence</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Hypertension</td>
<td>Mortality and cardiovascular events</td>
<td>--</td>
<td>• There were no head-to-head RCTs.</td>
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</table>
|                    | Blood pressure control and quality of life    | Good                      | • One 24-week RCT (n=379) showed equivalent efficacy for blood pressure control with captopril and enalapril, but statistically significantly better quality of life with captopril than with enalapril.\(^\text{15}\)  
• Another 8-week RCT (n=360) showed no significant difference in efficacy for blood pressure control or quality of life with captopril and enalapril.\(^\text{16}\) |
| Recent myocardial infarction (MI) | Mortality and cardiovascular events | Fair                  | • One RCT (n=225) showed a significant difference in mortality rates for captopril vs. enalapril after 90 days (12% vs. 1%, \(p=0.038\)) and 12 months (13% vs. 3%, \(p=0.022\)).\(^\text{17}\)  
• Another RCT (n=212) comparing captopril with perindopril found no significant differences in mortality rates at 6 months (13% vs. 6%, \(p=0.12\)).\(^\text{18}\)  
• Neither trial reported rates of symptomatic heart failure as an endpoint. |
| Heart failure      | Mortality and hospitalizations for heart failure | Fair                  | • One RCT (n=254) showed no significant difference in total mortality between fosinopril and enalapril at 12 months (1.6% vs. 4.6%, \(p=\text{NS}\)).\(^\text{19}\)  
• In the same trial, a statistically significant decrease in combined hospitalization plus mortality was observed for patients in the fosinopril group compared with those in the enalapril group (19.7% vs. 25%, \(p=0.03\)).\(^\text{19}\) |
| Symptomatic improvement | Good                                          |                            | • There were 14 head-to-head RCTs reported in 15 publications.\(^\text{19-34}\) One of the trials was described in two different publications.\(^\text{26,27}\)  
There was no significant differences in improvement in NYHA class or exercise duration for captopril, enalapril, fosinopril, lisinopril, quinapril, and ramipril. In the included studies, sample sizes ranged from \(n=13\) to \(n=315\), and follow up periods ranged from 3 to 12 months.  
• There were no head-to-head RCTs of benazapril, trandolapril, or perindopril. |

ESRD= End-stage renal disease, NS= Non-significant, NYHA=New York Heart Association
Systematic reviews and meta-analyses

No systematic reviews or meta-analyses of head-to-head trials comparing the effectiveness of ACE inhibitors were identified.

Randomized controlled trials

One recent RCT was identified that directly compared ACE inhibitors. This study was published subsequent to the 2005 health technology assessment summarized above. Shankar and colleagues compared the efficacy and tolerability of trandolapril with that of enalapril in Indian patients with mild to moderate hypertension. In this double-blind, multicentre, parallel-group comparative clinical study, 120 patients with mild to moderate hypertension were randomly assigned to receive trandolapril 2 mg (n=61) or enalapril 5 mg (n=54) once daily for 8 weeks. The primary outcome measured was the attainment of a sitting diastolic blood pressure of less than 90 mmHg at the end of the eighth week. The secondary outcome measured was the attainment of a diastolic blood pressure of less than 90 mmHg or reduction of at least 10 mmHg in diastolic blood pressure compared with baseline at any visit. There was no significant difference in the proportion of patients who satisfied the primary outcome in the trandolapril (60/61 [98.4%]) versus the enalapril (50/54 [92.6%]) group, or in the proportion of patients who satisfied the secondary outcome at 2, 4, or 8 weeks. The authors reported that trandolapril was better tolerated than enalapril.

Observational studies

A retrospective study conducted in Quebec compared the effectiveness of different ACE inhibitors in improving survival after myocardial infarction (MI) in a Canadian cohort. The study used linked hospital discharge and prescription data from 18,453 patients 65 years of age and older who were admitted to 109 Canadian hospitals for acute MI between April 1, 1996 and March 31, 2000. The study cohort included 7,512 patients who had filled a prescription for an ACE inhibitor within 30 days of discharge and continued to receive the same drug for at least 1 year. After adjusting for potential confounding variables, it was found that patients who initially filled prescriptions for ramipril had a statistically significantly lower 1-year mortality rate than did patients who filled a prescription for enalapril, fosinopril, captopril, and quinapril; there were no significant differences in 1-year mortality between patients receiving ramipril and those receiving perindopril or lisinopril. With ramipril as the reference, the adjusted hazard ratios (HR) were: 1.47 (95% confidence interval [CI]: 1.14 to 1.89) for enalapril; 1.71 (95% CI: 1.29 to 2.25) for fosinopril; 1.56 (95% CI: 1.13 to 2.15) for captopril; 1.58 (95% CI: 1.10 to 2.28) for quinapril; 0.98 (95% CI: 0.60 to 1.60) for perindopril; and, 1.28 (95% CI: 0.98 to 1.67) for lisinopril. Thus, the study showed that in elderly survivors of MI, ramipril was associated with lower mortality rates within the first year of hospital discharge compared with most of the other ACE inhibitors.

A retrospective cohort study conducted by Tu and colleagues in Ontario used linked administrative databases on over 1.4 million residents to assess whether ramipril was superior to other ACE inhibitors after MI. The study included patients over 66 years of age who were admitted to the hospital for acute MI, survived more than 30 days after discharge, and were initiated on an ACE inhibitor and remained on the same ACE inhibitor from April 1997 to March 31, 2000. The study cohort (n=5,408) was followed for 2 years, and readmission for acute MI and mortality were measured. Compared with patients receiving enalapril, there was no significant difference for the combined end point of “readmission for acute MI or mortality” across users of ramipril (adjusted HR: 0.95 [95% CI: 0.79 to 1.15]), lisinopril (adjusted HR 1.02 [95% CI: 0.84 to 1.25]), or “other ACE inhibitors” (benazepril, captopril, cilazapril, fosinopril,
perindopril, quinapril, and trandolapril; adjusted HR 1.08 [95% CI: 0.88 to 1.32]). In conclusion, the findings of this study supported a class effect among ACE inhibitors in treatment after acute MI, as they found no advantage of any one ACE inhibitor over another in terms of readmission rates for acute MI or mortality.

Another retrospective cohort study by Tu et al., which used the same Ontario databases, examined the relative association between ACE inhibitors and readmission and mortality rates in patients with congestive heart failure (CHF). The study cohort included 6,753 patients with newly diagnosed CHF who had been admitted to hospital and survived more than 30 days after discharge and were initiated on an ACE inhibitor during that time period. Patients were followed for more than 2 years and were excluded from the analysis if they switched medications or discontinued the initial ACE inhibitor. The primary outcome of interest was the combined end point of readmission for CHF as a primary diagnosis or mortality. The secondary outcomes were CHF readmission alone and mortality alone. Relative to enalapril users, no significant difference in the primary combined end point was observed in users of lisinopril (adjusted HR 1.08 [95% CI: 0.94 to 1.23]), ramipril (adjusted HR 1.06 [95% CI: 0.92 to 1.24]), or “other ACE inhibitors” (benazepril, captopril, cilazapril, fosinopril, perindopril, quinapril, and trandolapril; adjusted HR 1.02 [95% CI: 0.90 to 1.17]). No significant differences among groups were observed in the secondary end points. The authors concluded that there were no significant differences among the various ACE inhibitors for patients with newly diagnosed CHF initiated on ACE inhibitors in terms of CHF readmission or mortality, either separately or combined, suggesting a class effect of ACE inhibitors in the treatment of patients with CHF.

A recent retrospective cohort study conducted in Denmark analyzed the risk of death or recurrent MI among patients treated with ACE inhibitors (trandolapril, ramipril, enalapril, captopril, and perindopril) following initial hospitalization for MI, using individual-level linkage of nationwide administrative registries. The study cohort included 16,068 patients over 30 years of age who had been hospitalized for an initial MI between 1995 and 2002, had survived at least 30 days after discharge, and had filled at least one prescription for an ACE inhibitor. The predefined end-points of interest were mortality due to all causes and readmission due to recurrent MI. Adjusted Cox regression analysis demonstrated no statistically significant differences in risk for all-cause mortality between different ACE inhibitors, and only captopril was associated with a higher risk of reinfarction (trandolapril as reference; HR 1.18 [95% CI]: 1.05 to 1.34); however, following adjustment for differences in used dosages, this comparison became nonsignificant (HR 0.95 [95% CI]: 0.83 to 1.08). The study had the following main findings: (i) when used in comparable dosages, all the ACE inhibitors tested had similar clinical efficacy in reducing mortality and recurrent MI rates; (ii) used dosages in healthcare were low compared with clinical trials, and in this study patients using captopril were the most underdosed; and, (iii) the dosages used appeared to influence clinical efficacy, and using an appropriate dosage was important to achieve the full benefits of treatment. The authors concluded that treatment at the recommended dosage is more important than which ACE inhibitor is used.

Limitations

The studies included in the present review consisted of one HTA published in 2005, one small head-to-head RCT which was published since the HTA was conducted, and four recent medium to large observational studies. The main limitation of this review is the lack of large long-term RCTs comparing the effectiveness of different ACE inhibitors for clinically important outcomes such as a reduction in mortality. Unfortunately, such trials are not likely to be conducted because of the enormous size and expense of a comparative trial that would be...
powered to detect differences in survival, or other cardiovascular outcome measures, such as recurrent MI rates, between the individual ACE inhibitors.

On the other hand, observational cohort studies, such as the ones identified above, allow the assessment of the effect of medications in real-life situations, in contrast to the highly selected samples of RCTs. However, cohort studies are prone to biases and confounded by factors such as differences in patient characteristics and the severity of the indication. Other limitations in the included cohort studies include those that are inherent to the use of administrative databases, such as patient drug adherence, the lack of consideration for dosing variation among ACE inhibitors, and the lack of detailed information on important cardiovascular risk factors that may affect cardiovascular outcomes, such as body mass index, alcohol, and smoking.

**Conclusions and implications for decision or policy making:**

A number of studies were identified that compared different ACE inhibitors for the treatment of patients with hypertension, recent myocardial infarction, and congestive heart failure. However, studies comparing the effectiveness of different ACE inhibitors for kidney protection were lacking. Although there is limited evidence that not all ACE inhibitors are equally efficacious for various outcomes including blood pressure control, and mortality rates post MI, the majority of the available trials suggest that there is no clear advantage of using one ACE inhibitor over another. Until more conclusive evidence is available, formulary decisions should also take clinical experience and acquisition costs into consideration.

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