Comparative effectiveness of ACE inhibitors and angiotensin receptor blockers in patients with prior myocardial infarction

Dennis Ko, Paymon Azizi, Maria Koh, Alice Chong, Peter Austin, Therese Stukel, Cynthia Jackevicius

ABSTRACT

Objective Although ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly prescribed for patients with coronary artery disease, whether these medications are similarly effective is still a subject of intense debate. Our objective was to compare the clinical effectiveness of ACEIs and ARBs in patients with prior myocardial infarction (MI).

Methods All residents older than 65 years, alive on 1 April 2012, with a prior MI were included. Propensity weighting was used to balance potentially confounding baseline covariates between the treatment groups. The primary outcome was a composite of cardiovascular death, hospitalisation for MI or unstable angina at 3 years.

Results Our cohort included 59 353 patients with MI; their mean age was 77 years and 40% were women. In the propensity-weighted cohort, the primary outcome occurred in 6.5% in the ACEI group and 5.7% in the ARB group at 1 year (HR comparing ACEI with ARB 1.14; 95% CI 1.05 to 1.23, p<0.001). At 3 years, the primary outcome occurring in 16.0% with ACEIs and 15.1% with ARBs (HR 1.07; 95% CI 1.02 to 1.12; p<0.001). A significant interaction with sex was observed, with women prescribed ACEIs having a higher hazards (HR 1.17; 95% CI 1.10 to 1.23, p<0.001). At 3 years, the primary outcome occurred in 6.5% in the ACEI group and 5.7% in the ARB group, with no significant difference was seen among men (HR 1.00; 95% CI 0.93 to 1.06, interaction p<0.001).

Conclusions Despite previous concerns regarding ARBs, we found that they had slightly lower rates of adverse clinical cardiovascular outcomes among older patients with MI compared with ACEIs. The observed difference in clinical outcomes may be related to a sex difference in effectiveness.

INTRODUCTION

Medications that inhibit the renal angiotensin aldosterone system such as ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly recommended to treat patients with myocardial infarction (MI). Although more than 100 randomised trials have enrolled more than 250 000 patients without heart failure to study ACEIs and ARBs, whether these medications are similarly effective in a broad range of patients with cardiovascular conditions continues to be a subject of intense debate. The term ‘ARB–MI paradox’ was coined after the Valsartan Antihypertensive Long-Term Use Evaluation trial demonstrated a 19% significantly increased risk of MI in the valsartan group as compared with amlodipine among patients with hypertension at high cardiovascular risk. This controversy sparked the efforts of numerous investigators to combine all available data to understand the safety and effectiveness of ACEIs relative to that of ARBs. Findings have diverged substantially, with some data showing ACEIs are associated with improved outcomes compared with ARBs, while other data show ACEIs are not significantly different from ARBs. Some
studies have even concluded that ARBs are not signifi-
cantly different compared with placebo.\textsuperscript{8,9,11}

One of the difficulties in comparing the safety and
effectiveness of ACEIs relative to ARBs is the paucity of
head-to-head clinical trials. In fact, only three large trials
have directly compared ACEIs and ARBs in patients
with coronary artery disease.\textsuperscript{12-14} Of these trials, two
enrolled patients had acute MI complicated with heart
failure,\textsuperscript{12,15} and the other enrolled patients were at high
risk of vascular events.\textsuperscript{14} Moreover, two of these trials were
conducted close to two decades ago.\textsuperscript{12,13} It is difficult to
know whether the results of these older trials are still
applicable in contemporary clinical practice. Given that
ACEIs and ARBs are commonly prescribed in the treat-
ment of patients with cardiovascular disease, we sought
to address this gap in knowledge by comparing the real-
world effectiveness of ACEIs and ARBs in a large popu-
lation-based cohort with prior MI using longitudinal linked
databases in Ontario, Canada.

METHODS

Design and data sources
We conducted a retrospective cohort study using popu-
lation-based databases in Ontario, Canada. The Cardi-
ovascular Health in Ambulatory Care Research Team
(CANHEART) cohort was created by merging 17 different
longitudinal individual-level data sources.\textsuperscript{15} The data
sources used for this study have been described previously
with additional information on our study website (www.
canheart.ca).\textsuperscript{15-19} Primary databases that were used for this
study include (1) Ontario Health Insurance Plan, a registry
of all physician billings in Ontario; (2) Ontario Drug
Benefit, a registry of outpatient prescriptions; (3) Regis-
tered Persons Database of Ontario, a registry of the demo-
graphics of Ontario residents; (4) Canadian Institute for
Health Information (CIHI) Discharge Abstract Database, a
database used to identify prior cardiac risk factors, comor-
bidities and hospitalisations; (5) Statistics Canada census
data were used for neighbourhood income data; and (6)
Office of the Registrar General Deaths database was used to
ascertain cause of death. These datasets were linked using
unique encoded identifiers and analysed at the Institute for
Clinical Evaluative Sciences.

Study sample
Ontario residents who were alive on 1 April 2012 (index
date), older than 65 years and had a valid health insur-
ance number were eligible for inclusion in the study
cohort. Patients who were prescribed an ACEI or an ARB
in the 100 days before 1 April 2012 were considered for
inclusion. An age limit was used in our study because the
Ontario Drug Benefit database includes only prescription
drug information for those aged 65 years and above. The
cohort was defined as those who had a hospitalisation for
MI in the 10 years prior to the index date using Interna-
tional Classification of Disease 10th version codes I21 and
I22.

ACEIs and ARBs
ACEIs and ARBs that were available on the Ontario drug
formulary within 100 days of the index date were included
in the study. ACEIs included were benazepril, captopril,
cilazapril, enalapril, fosinopril, lisinopril, perindopril,
quinapril, ramipril and trandolapril. The ARB group
included candesartan, eprosartan, irbesartan, losartan,
olmesartan, telmisartan and valsartan. Different formu-
lations (eg, enalapril maleate and enalapril sodium) and
manufacturers (ie, brand and generic) were grouped
together, while intravenous drugs were excluded. Combi-
nation drugs were treated as ACEIs or ARBs, depending
on the respective formulation.

Outcomes
The primary outcome of this study was a composite of
cardiovascular mortality, hospitalisation for MI and
unstable angina at 3 years. We also examined this
composite outcome at 1 year. Secondary outcomes
included hospitalisation for MI or angina, and hospital-
isation for heart failure at 1 and 3 years. Cardiovascular
mortality was ascertained by the Office of the Registrar
General Deaths database. Hospitalisation for cardiac
conditions was ascertained by CIHI discharge abstract
database.

Statistical analysis
Demographic and clinical characteristics of patients
prescribed ACEIs and ARBs were compared using \( \chi^2 \)
tests for categorical variables and the Wilcoxon rank-sum
test for continuous variables. To adjust for potential
confounding between the treatment groups, we used
the inverse probability of treatment weighting using
the propensity score to account for observed systematic
differences in baseline covariates between treatment
groups.\textsuperscript{20,21} The propensity score, which was defined as
the probability of receiving ACEIs, was estimated using
a logistic regression model in which treatment group
(ACEI vs ARB) was regressed on the following charac-
teristics related to the likelihood of being prescribed
one of the drugs: demographics (age, sex, income, rural
residency), timing of MI from index data, cardiac risk
factors (hypertension, diabetes, hyperlipidemia), cardio-
vascular conditions (atrial arrhythmia, cerebrovascular
disease, heart failure, peripheral vascular disease, shock)
and medical comorbidities (anaemia, cancer, chronic
obstructive pulmonary disease, liver disease, peptic ulcer
disease, renal disease), cardiac procedures (cardiac cathe-
terisation, percutaneous coronary intervention, coronary
arterial bypass grafting) and prior medication (statins,
beta blockers, diuretics, clopidogrel, calcium channel
blockers, long-acting nitrates, warfarin).

Patients were then weighted by the inverse of the proba-
bility of receiving the treatment that they received.\textsuperscript{20}
Balance of baseline covariates between the treatment
groups in the weighted cohort was assessed by computing
weighted standardised differences, with differences of less
than 0.1 indicating good balance.\textsuperscript{22} The effect of ACEIs
Cardiac risk factors and prevention

Characteristics before and after propensity weighting

Prior to propensity score weighting, patients prescribed ARBs were slightly older (77.4 years vs 76.9 years), had higher rates of cardiac risk factors, including diabetes (49.2% vs 43.9%), hypertension (94.7% vs 88.6%), dyslipidemia (58.6% vs 55.3%) and renal disease (11.3% vs 8.3%), and higher Charlson score compared with those prescribed ACEIs (online supplementary table 2).

After propensity score weighting, the ACEI and the ARB group were well balanced, with the standardised differences being less than 0.1 for all characteristics (table 1). In the weighted sample, the mean age was 77, 59.5% of patients were men, 45.6% had diabetes, 90.4% had hypertension, 56.3% had dyslipidemia, 9.3% had renal disease and 26.2% had a history of heart failure. The majority of patients with MI patients were also prescribed statins (84.1%) and beta blockers (70.3%).

Clinical outcomes of ACEIs versus ARBs

At 1 year, the primary outcome of cardiovascular death or hospitalisation for MI or unstable angina occurred in 6.5% of patients in those taking ACEI and 5.7% in those taking ARB (HR 1.14; 95% CI 1.05 to 1.23; p<0.001) (table 2). This trend persisted at 3 years, with the primary outcome occurring in 16.0% of those taking ACEI and 15.1% of those taking ARB (HR 1.07; 95% CI 1.02 to 1.12; p=0.008). The corresponding Kaplan-Meier curve is shown in figure 2. The rate of cardiovascular death was significant higher in the ACEI group compared with the ARB group (table 2). At 1 year, cardiovascular death was 3.7% in the ACEI group and 2.8% in the ARB group (HR 1.31; 95% CI 1.18 to 1.45; p<0.001). At 3 years, cardiovascular death occurred in 9.9% of the ACEI group and in 8.6% of the ARB group (HR 1.16; 95% CI 1.09 to 1.23; p<0.001). We also observed lower all-cause mortality in the ARB group at 6.6% at 1 year (vs 8.2% in the ACEI group) and at 3 years (20.0% in the ARB group vs 22.4% in the ACEI group). There was no significant difference observed in hospitalisation for MI or angina, or heart failure at 1 or 3 years.

Subgroup analyses

We performed subgroup analyses to investigate the potential difference in clinical outcomes between ACEIs and ARBs among predefined subgroups (table 3). Subgroup analyses based on age, diabetes status and prior heart failure did not show any significant interaction. In contrast, a significant sex difference was observed in which women had a higher HR associated with ACEIs (1.17; 95% CI 1.10 to 1.26), while there was no significant difference between the treatment groups among men (HR 1.00; 95% CI 0.93 to 1.06, p=0.001 for interaction). To explore this potential discrepancy, we further explored...
Table 1  Baseline characteristics after propensity score weighting

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ACEIs (%)</th>
<th>ARBs (%)</th>
<th>Standardised difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>77.0±9.5</td>
<td>77.1±14.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Men</td>
<td>59.6</td>
<td>59.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Rural resident</td>
<td>15.7</td>
<td>15.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Timing of MI in months, mean±SD</td>
<td>53.7±42.5</td>
<td>54.0±65.0</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Cardiovascular comorbidities

- Chronic ischaemic heart disease: 82.5 vs. 82.1, 0.011
- Angina: 24.6 vs. 26.2, 0.037
- Atrial fibrillation/flutter: 22.2 vs. 22.4, 0.005
- Diabetes: 45.5 vs. 45.6, 0.003
- Heart failure: 26.1 vs. 26.5, 0.008
- Hypertension: 90.4 vs. 90.4, 0.001
- Dyslipidemia: 56.3 vs. 56.2, 0.001
- Peripheral vascular disease: 7.1 vs. 7.2, 0.002
- Cerebrovascular disease: 9.4 vs. 9.4, <0.001
- Stroke/transient ischaemic attack: 7.7 vs. 7.7, <0.001
- Shock: 5.0 vs. 4.9, 0.002

Medical comorbidities

- Renal disease: 9.2 vs. 9.3, 0.004
- Cancer: 11.1 vs. 11.1, 0.001
- Chronic obstructive pulmonary disease: 13.3 vs. 13.3, <0.001
- Liver disease: 1.0 vs. 1.0, <0.001
- Peptic ulcer disease: 4.0 vs. 4.0, 0.001
- Anaemia/blood disease: 22.1 vs. 22.4, 0.006
- Charlson score, mean±SD: 2.9±2.4 vs. 2.9±3.6, 0.006

Prior cardiac invasive procedures

- Percutaneous coronary intervention: 46.8 vs. 46.5, 0.006
- Coronary artery bypass grafting: 20.4 vs. 20.5, 0.002
- Coronary catheterisation: 80.7 vs. 80.4, 0.005

Medication use

- Statins: 84.0 vs. 84.1, 0.001
- Beta blocker: 70.3 vs. 70.3, 0.001
- Diuretics: 43.8 vs. 43.8, <0.001
- Clopidogrel: 31.4 vs. 31.1, 0.006
- Calcium channel blockers: 30.5 vs. 30.5, <0.001

Table 1  Continued

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ACEIs (%)</th>
<th>ARBs (%)</th>
<th>Standardised difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>19.2</td>
<td>19.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Warfarin</td>
<td>12.3</td>
<td>12.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Spirolactone</td>
<td>5.2</td>
<td>4.5</td>
<td>0.030</td>
</tr>
</tbody>
</table>

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; MI, myocardial infarction.

Potential difference in dosages and medication adherence by sex. The median dosage of ramipril in women was 5 mg, while the median dosage was 7.5 mg in men. In contrast, median dose of ARBs was identical between men and women. Women appeared to have higher adherence for ARBs than ACEIs. The proportional days covered for ACEI was 74.9% in women and 77.4% in men, and 76.8% for ARB in women and 75.9% in men.

**DISCUSSION**

Using a population-based level big data cohort in Ontario, Canada, we performed a comprehensive evaluation comparing the clinical outcomes of ACEIs versus ARBs in patients with prior MI. Despite the concern of an ARB–MI paradox and that it may not be effective in coronary artery disease, we found that ARBs were actually associated with slightly lower rates of cardiovascular death as compared with patients treated with ACEI. Heterogeneity in the treatment effects was seen in that women had a significantly lower risk of events when prescribed ARBs compared with ACEIs, while there was no difference in the primary outcome between ACEI and ARB groups for men. Our findings should help alleviate concerns regarding the potential harmful effects associated with ARBs.

It has been widely believed that ACEIs are more effective than ARBs in a broad range of patients with cardiovascular diseases. Practice guidelines have consistently recommended using ARBs only when patients are not able to tolerate the side effects associated with ACEIs. Recently, Messerli and colleagues has challenged this conventional wisdom. They pointed out that the relatively efficacy of ACEIs and ARBs was mainly derived from comparisons of trials that compared ACEIs versus placebo, and ARBs versus placebo. Given the fact that trials of ACEIs were conducted almost a decade before ARBs, the enrolled patients were rarely treated with statin therapy or other optimal medical therapy, and had almost twice the event rates of patients enrolled in trials of ARBs. As a result, it is very plausible that the temporal discrepancy in ACEI and ARB trials may explain why ACEIs have previously been shown to have larger benefits as compared with ARBs.

**Prior studies of ACEI versus ARBs in MI**

Indeed, the three landmark trials that performed head-to-head comparisons between ACEIs and ARBs—Valsartan in Acute Myocardial Infarction (VALIANT), Optimal
Table 2  Outcomes in the ACEI and ARB group

<table>
<thead>
<tr>
<th></th>
<th>ACEI rate (%)</th>
<th>ARB rate (%)</th>
<th>ARB rate (%)</th>
<th>Forest plot</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1-year follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>3.7</td>
<td>2.8</td>
<td>1.31 (1.18–1.45)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CV death/hospitalisation for MI or angina</td>
<td>6.5</td>
<td>5.7</td>
<td>1.14 (1.05–1.23)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation for MI or angina</td>
<td>3.4</td>
<td>3.4</td>
<td>1.01 (0.92–1.12)</td>
<td>0.791</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td>3.3</td>
<td>3.2</td>
<td>1.03 (0.93–1.14)</td>
<td>0.541</td>
<td></td>
</tr>
<tr>
<td><strong>3-year follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>9.9</td>
<td>8.6</td>
<td>1.16 (1.09–1.23)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CV death/hospitalisation for MI or angina</td>
<td>16.0</td>
<td>15.1</td>
<td>1.07 (1.02–1.12)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation for MI or angina</td>
<td>8.1</td>
<td>8.3</td>
<td>0.98 (0.92–1.05)</td>
<td>0.552</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td>8.2</td>
<td>8.2</td>
<td>1.00 (0.94–1.07)</td>
<td>0.984</td>
<td></td>
</tr>
</tbody>
</table>

Higher HR indicates better outcomes associated with ARBs.

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; MI, myocardial infarction.

![Figure 2](http://openheart.bmj.com/)

Figure 2  Kaplan-Meier curve of the primary outcome in patients prescribed ACE inhibitor (ACEI) and angiotensin receptor blocker (ARB). Y-axis shows event rate rates and x-axis shows time in days after assembling the study cohort. Blue line depicts event rates for ACEI and red line depicts event rates for ARBs.

Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL), and ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)—all showed no significant outcome difference between patients prescribed ACEIs and ARBs. While findings from our study may appear at odds with these trials, patients included in our study differed substantially from prior trials. First, the mean age of our cohort was more than 10 years older than these clinical trials and we had significantly higher proportion of women at 40% as compared with these three trials that ranged from 27% to 32%. Second, we included patients who had prior MI in the past 10 years while VALIANT and OPTIMAAL were trials of acute MI with heart failure. Finally, the use of statins has substantially increased where we observed 84% prescription in our cohort; the OPTIMAAL trial reported only about 30% were prescribed statins.

An emerging number of observational studies have suggested that outcomes of patients treated with ARBs may have better outcomes compared with ACEIs. Using the Reduction of atherothrombosis for Continued Health registry, Potier and colleagues performed an analysis including 40,625 patients who were at high cardiovascular risk and found a 10% reduction in the risk of a composite of cardiovascular mortality, MI, stroke or hospitalisation with ARB compared with ACEI at 4 years. Similarly, Padwal et al evaluated 87,772 diabetic patients without prior MI using a large US claims database and found that ARBs were associated with a 10% reduction in all-cause mortality and all-cause hospitalisation. A smaller study from Korea also demonstrated that ARBs may be associated with improved clinical outcomes in patients with MI without heart failure or ventricular dysfunction. By focusing on patients with prior MI, our study adds to the contemporary literature to suggest potential benefits associated with ARBs as compared with ACEIs.

Sex difference of ACEI and ARB

We are unaware of any studies that have evaluated the potential sex difference between ACEIs and ARBs among patients with coronary artery disease. An observational study that evaluated sex difference between ACEIs and ARBs in patients with heart failure also found that women had significant survival improvement with ARBs, but not in men. In our study, we found that women were prescribed lower dose of ramipril relative to men. Second, we also found that women have greater adherence to ARBs as compared with ACEIs. Others have postulated that women have greater response in blood pressure reduction in ARBs as a potential mechanism.
of sex difference, and there is a diminishing effect of ACEI in women over time. However, since this was an incidental finding, we are cautious with respect to its interpretation and suggest future study for additional investigations.

**Study limitations**

Several potential limitations of our study merit consideration. First, despite the availability of a large amount of clinical detail and using sophisticated propensity weighting, it is still possible that the difference we observed between the treatment groups was a result of selection bias. However, the influence of selection bias is likely to be greater in studies comparing an active intervention with no treatment than in studies like ours that compared two active interventions with similar indications. Furthermore, in our study, patients prescribed ARBs were sicker prior to propensity weighting, as they were older and had more comorbidity, indicating that ARBs were not selectively prescribed to lower-risk patients with MI. Second, we did not have information regarding whether patients were prescribed ARBs because of side effects associated with ACEIs and whether they were prescribed as first-line therapy. Therefore, our study should not be interpreted as advocating ARBs should be a first-line therapy in patients with MI. Third, due to the number of formulations of ACEIs and ARBs on the market, we combined medications into two groups so that we can perform our analyses. Our finding may not be applicable to all jurisdictions if the composition of these medications is vastly different. Finally, our study only included patients over 65 years of age because of the unavailability of prescription information on younger patients. Further studies are needed to examine whether similar results are seen among younger patients.

**CONCLUSIONS**

Although many are still concerned with an ARB–MI paradox, our study of close to 60 000 patients with MI should serve as reassurance that ARBs are not associated with adverse outcomes compared with ACEIs. Potential benefits of ARBs as compared with ACEIs in older women with MI should be further evaluated.

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**Competing interests** None declared.

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**Data sharing statement** Data may be obtained from a third party and are not publicly available.

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