Is *Ramipril* Really Better Than Other Angiotensin-Converting Enzyme Inhibitors After Acute Myocardial Infarction?

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Whether angiotensin-converting enzyme (ACE) inhibitors are interchangeable and equally efficacious after acute myocardial infarction (AMI) is controversial. We assessed whether ramipril was superior to other ACE inhibitors after AMI as suggested by a previously published study. We performed a retrospective cohort study using linked administrative databases on >1.4 million elderly residents in the province of Ontario who were admitted to the hospital for AMI, survived ≥30 days after discharge, and were initiated on an ACE inhibitor after AMI and remained on the same ACE inhibitor from April 1, 1997 to March 31, 2000. We followed patients for 2 years and measured readmission for AMI or mortality, together or alone. Our cohort included 5,408 elderly patients. Compared with patients on enalapril, there was no significant difference for the combined end points of readmission for AMI or mortality across users of ramipril (adjusted hazard ratio 0.95, 95% confidence interval 0.79 to 1.15), lisinopril (adjusted hazard ratio 1.02, 95% confidence interval 0.84 to 1.25), or other ACE inhibitors (adjusted hazard ratio 1.08, 95% confidence interval 0.88, 1.32). In conclusion, the findings of this study support a class effect among ACE inhibitors in treatment after AMI. **(Am J Cardiol 2006;98: 6–9)**

A study done in Quebec[1] that compared the benefits of various angiotensin-converting enzyme (ACE) inhibitors after acute myocardial infarction (AMI) concluded that ramipril was associated with lower mortality than were other ACE inhibitors. This study used administrative data in the province of Quebec to compare the efficacy of the various ACE inhibitors. We set out to verify the findings of this study supporting the superiority of ramipril over other ACE inhibitors after AMI.

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We performed a retrospective cohort study in >1.4 million elderly residents in Ontario by using administrative databases that were linked anonymously through encrypted unique patient identifiers. We included all patients who were ≥66 years of age with a discharge diagnosis of AMI recorded in the Canadian Institute for Health Information hospital discharge database from April 1, 1997 to March 31, 2000 using *International Classification of Diseases, Ninth Revision* code 410 as the most responsible diagnosis or as an in-hospital complication. Previous studies have shown the use of administrative data are highly accurate for AMI coding.[2–4]. Patients were excluded if their total length of stay was <3 days (to include only patients with true AMI rather than unstable angina), they were transferred from another hospital, they died in the hospital or within 30 days after discharge (to avoid survival treatment selection bias),[5] or they had an admission for AMI 3 years previously. Patients were also excluded if they were not prescribed an ACE inhibitor within 30 days after discharge or they were prescribed an ACE inhibitor or angiotensin II receptor blocker in the year before hospital admission according to the Ontario Drug Benefit database, which records prescriptions filled by residents in Ontario who are ≥65 years of age. Patients were categorized as initiated on enalapril, ramipril, lisinopril, or other ACE inhibitors (benazepril, captopril, cilazapril, fosinopril, perindopril, quinapril, and trandolapril).

Patients were followed for 2 years after their discharge date. Patients were censored if they had the event of interest (i.e., death or readmission for AMI); they were switched to an ACE inhibitor different from what was initially dispensed, they discontinued the ACE inhibitor they were initially prescribed, or they reached the end of the observation period (March 31, 2002). As in other studies,[6] we used the "days supplied" variable of the Ontario Drug Benefit database to estimate the intended duration of each prescription. If patients were dispensed the particular ACE inhibitor before the end of this period, the excess drug supply was carried over to the next prescription's day's supply estimation. Patients were allowed a 20% grace period on the previous days supplied to refill the next prescription. If they did not refill their prescription within these successive pe-

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Table 1
Baseline characteristics, hospitalization, procedure, and drug utilization history

Characteristic	Drug Group			
	Enalapril (n = 1,745)	Ramipril (n = 1,479)	Lisinopril (n = 1,085)	Other ACE Inhibitors (n = 1,099)
Age (yrs), mean ± SD	75.6 ± 6.4	74.9 ± 6.3	74.8 ± 6.0	75.3 ± 6.4
Women	37.2%	39.1%	34.7%	39.5%
Long-term care	0.9%	0.3%	0.6%	0.7%
Hospitalizations (3 yrs before index event)				
Congestive heart failure	2.2%	2.1%	1.8%	3.3%
Ischemic heart disease	10.4%	10.1%	10.1%	10.7%
Renal failure	4.0%	5.1%	3.5%	4.8%
Stroke	0.1%	0.1%	0.0%	0.3%
Procedures (3 yrs before index event)				
Angiography	1.8%	2.0%	1.5%	1.5%
Coronary bypass	0.7%	0.5%	1.0%	0.9%
Echocardiography	15.7%	19.8%	15.5%	15.5%
Coronary angioplasty	8.6%	17.0%	10.1%	8.1%
Valve surgery	0.0%	0.1%	0.1%	0.0%
Drug utilization (1 yr before index event)				
α Blockers	4.6%	3.9%	4.1%	4.4%
Antiarrhythmics	2.0%	2.2%	1.9%	1.4%
Anticoagulants	4.0%	5.0%	5.3%	3.9%
Antidiabetics	18.3%	16.6%	18.0%	17.4%
Antiplatelets	1.4%	1.3%	1.2%	1.5%
Antirheumatics	1.3%	0.8%	0.8%	1.1%
Aspirin	23.3%	22.1%	21.1%	22.9%
β Blockers	24.0%	24.1%	22.0%	21.2%
Calcium channel blockers	31.5%	30.3%	28.5%	31.9%
Digoxin	6.9%	5.4%	6.2%	6.0%
Diuretics	13.8%	14.3%	15.1%	14.0%
Hydralazine	0.3%	0.1%	0.2%	0.0%
Inhalers	3.3%	14.0%	13.3%	13.6%
Lipid-lowering drugs	13.2%	18.1%	15.9%	14.6%
Loop diuretics	9.5%	8.2%	8.1%	9.7%
Nitrates	26.3%	25.6%	20.7%	27.2%
Nonsteroidal anti-inflammatory drugs	23.3%	23.7%	24.2%	24.9%
Other antihypertensives	1.2%	0.7%	1.0%	1.3%
Spironolactone	1.4%	1.6%	0.9%	1.6%

riods, they were deemed to have discontinued the ACE inhibitor.

The primary outcome of interest was the combined end point of readmission for AMI as a primary diagnosis or mortality. The secondary outcomes were AMI readmission alone and mortality alone. Time-to-event analyses were conducted for AMI hospitalization by using Cox's proportional hazards models, with enalapril users as the reference group, after controlling for all covariates listed in Table 1 and the fiscal quarter of the index date to account for temporal effects. As an overall measurement of co-morbidity, we controlled for the number of distinct drugs dispensed in the year before the index date,[7] Charlson's co-morbidity index,[8] and the presence of diabetes.[9] The proportional hazards assumption for each exposure variable was assessed in each analysis. All analyses were performed with SAS 8.2 for UNIX (SAS Institute, Cary, North Carolina). All statistical tests were performed at the 5% level of significance and were 2-sided.

In total, 5,408 patients with AMI who were initiated on an ACE inhibitor met our inclusion/exclusion criteria, with 32% on enalapril, 27% on ramipril, 20% on lisinopril, and 20% on another ACE inhibitor. Fewer than 1% of patients dwelled in long-term care facilities and >60% were men, overall and in each drug group. Baseline characteristics, hospitalizations for other conditions, procedures, and drug utilization were generally well balanced across groups (Table 1).

Seven hundred sixty patients (14%) were readmitted for an AMI or died within 2 years of entry into the cohort. In all, there were 223 deaths (4%) and 595 readmissions (11%) for an AMI. Death or readmission values per 100 person-years were 14.0 for enalapril, 11.7 for ramipril, 12.8 for lisinopril, and 15.5 for other ACE inhibitors.

Compared with patients on enalapril, we found no significant difference for the combined end points of readmission for AMI or mortality across users of ramipril (adjusted hazard ratio 0.95, 95% confidence interval 0.79 to 1.15), lisinopril (adjusted hazard ratio 1.02, 95% confidence interval 0.84 to 1.25), or other ACE inhibitors (adjusted hazard

Table 2
Readmissions or mortality, readmissions alone, or mortality alone

Characteristic	Drug Group			Other ACE Inhibitors
	Enalapril	Ramipril	Lisinopril	
Readmissions or mortality				
Follow-up time (d), mean ± SD	368 ± 286	424 ± 290	412 ± 291	336 ± 293
Death or readmission, n (%)	247 (4.6)	200 (3.7)	156 (2.9)	157 (2.9)
Death or readmission per 100 person-yrs	14.0	11.7	12.8	15.5
Crude HR (95% CI)	1	0.87 (0.72–1.05)	0.94 (0.77–1.15)	1.07 (0.88–1.31)
Adjusted HR (95% CI)	1	0.95 (0.79–1.15)	1.02 (0.84–1.25)	1.08 (0.88–1.31)
Readmissions alone				
Follow-up time (d), mean ± SD	368 ± 286	424 ± 290	412 ± 291	336 ± 293
Readmissions, n (%)	190 (3.5)	151 (2.8)	125 (2.3)	129 (2.4)
Readmissions per 100 person-yrs	10.8	8.8	10.2	12.7
Crude HR (95% CI)	1	0.87 (0.70–1.07)	0.99 (0.79–1.24)	1.14 (0.91–1.43)
Adjusted HR (95% CI)	1	0.93 (0.75–1.15)	1.13 (0.91–1.42)	1.13 (0.91–1.42)
Mortality alone				
Follow-up time (d), mean ± SD	395 ± 283	454 ± 283	442 ± 283	362 ± 293
Deaths, n (%)	74 (1.4)	67 (1.2)	42 (0.8)	40 (0.7)
Deaths per 100 person-yrs	3.9	3.6	3.2	3.7
Crude HR (95% CI)	1	0.92 (0.66–1.28)	0.81 (0.55–1.18)	0.93 (0.63–1.37)
Adjusted HR (95% CI)	1	1.07 (0.77–1.50)	0.97 (0.66–1.42)	0.93 (0.63–1.36)

CI = confidence interval; HR = hazard ratio.

ratio 1.08, 95% confidence interval 0.88, 1.32). We also found no significant difference in readmissions for AMI alone or mortality alone (Table 2).

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The findings of our study support a class effect among patients discharged with a diagnosis of AMI in terms of readmission rates for AMI or mortality because we found no advantage of any 1 ACE inhibitor over another in this regard. These results are consistent with a similarly conducted study that compared ACE inhibitor efficacy in patients with heart failure[10] and a class effect of ACE inhibitors seen in regression of ventricular and vascular hypertrophies.[11] Our results do not show the superiority of ramipril in AMI, in distinct contradiction to the study performed in Quebec.[1] It is likely that these conflicting results are due to a combination of differences in analytic techniques and differences in patient characteristics. The Quebec study reported only 1-year mortality, despite median follow-up times >1 year in each group assessed. It is not clear whether they mandated a maximum observation period for each patient in their study. We followed all our patients for up to 2 years maximum after the index AMI admission for the outcomes of interest and censored patients who did not remain on the initiated ACE inhibitor. The Quebec study also reported 2 separate methods of examining adherence indirectly by using a variable indicating the intended duration of drug therapy. In our study, this variable was the primary direct measurement of drug adherence. We eliminated patients who died within 30 days of discharge to avoid survivor treatment selection bias. We also excluded patients who were on an ACE inhibitor or angiotensin II receptor blocker 1 year before the index AMI admission to limit our study cohort to those patients who were prescribed an ACE inhibitor for treatment after AMI rather than for treatment of pre-existing congestive heart failure.

There are several limitations that we acknowledge and are inherent to the use of administrative databases in answering clinical questions. With our data we are only able to assume drug adherence when using the days supplied variable and repeat prescriptions; however, the assumptions used for estimating drug adherence were uniform across the different drugs. Our data do not contain information on other important cardiovascular risk factors that may affect cardiovascular outcomes such as body mass index, alcohol, and smoking. There is no reason to suspect that these patient characteristics were different for different drugs. Ramipril users had higher rates of angioplasty and use of lipid-lowering drugs, which could suggest that they were sicker but could also suggest that they were treated more aggressively. Despite these dissimilarities, the crude and adjusted hazard ratios detected no difference and we had >90% power to detect a 20% relative risk decrease in the primary outcome across groups. We did not account for dosing variation among the ACE inhibitors but simply examined the actual usage of drugs as in routine clinical practice.

Although our study was not the first to compare efficacy of ACE inhibitors in the treatment of AMI, our results conflict with the previously conducted study. Our results suggest that a class effect likely exists among ACE inhibitors and therefore possible improved efficacy of 1 ACE inhibitor over another should not be of concern when prescribing an ACE inhibitor in the treatment of AMI.

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