Mortality Rates in Elderly Patients Who Take Different Angiotensin-Converting Enzyme Inhibitors after Acute Myocardial Infarction: A Class Effect?

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Background: **Several randomized, controlled trials show that angiotensin-converting enzyme (ACE) inhibitors improve survival in patients who have had an acute myocardial infarction. However, existing data from trials do not address whether all ACE inhibitors benefit patients similarly.**

Objective: **To evaluate whether all ACE inhibitors are associated with similar mortality in patients 65 years of age or older who have had an acute myocardial infarction.**

Design: **Retrospective cohort study that used linked hospital discharge and prescription databases containing information on 18 453 patients 65 years of age or older who were admitted for an acute myocardial infarction between 1 April 1996 and 31 March 2000.**

Setting: **109 hospitals in Quebec, Canada.**

Patients: **7512 patients who filled a prescription for an ACE inhibitor within 30 days of discharge and who continued to receive the same drug for at least 1 year.**

Measurements: **The association between the specific drugs and clinical outcomes was measured by using Cox proportional hazards models, with adjustment for demographic, clinical, physician, and hospital variables and dosage categories, represented by time-dependent variables.**

Results: **Enalapril, fosinopril, captopril, quinapril, and lisinopril were associated with higher mortality than was ramipril; the adjusted hazard ratios and 95% CIs were 1.47 (95% CI, 1.14 to 1.89), 1.71 (CI, 1.29 to 2.25), 1.56 (CI, 1.13 to 2.15), 1.58 (CI, 1.10 to 2.82), and 1.28 (CI, 0.98 to 1.67), respectively. The adjusted hazard ratio associated with perindopril was 0.98 (CI, 0.60 to 1.60).**

Limitations: **The administrative databases did not contain detailed clinical information, and unmeasured factors associated with a patient's risk for death may have influenced physicians' prescription choices.**

Conclusion: **Survival benefits in the first year after acute myocardial infarction in patients 65 years of age or older seem to differ according to the specific ACE inhibitor prescribed. Ramipril was associated with lower mortality than most other ACE inhibitors.**

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See editorial comment on pp 157-158.

Many randomized, controlled trials have shown that the use of angiotensin-converting enzyme (ACE) inhibitors after the occurrence of an acute myocardial infarction improves survival and reduces the risk for a subsequent acute myocardial infarction (1–7). Although not all ACE inhibitors have been studied, they are invariably used in practice because physicians probably assume a class effect. A class effect implies that all drugs in a class exert the same effects, whether positive or negative, on their target population (8). Angiotensin-converting enzyme inhibitors have been shown to be effective in treating essential hypertension (9), renal disease (10), and left ventricular dysfunction (11), as well as in improving survival after acute myocardial infarction (12). Although beneficial effects might occur with all drugs in this class, the extent of benefit may vary with each drug (13). Moreover, the varying pharmacologic and structural characteristics of ACE inhibitors influence the potency and bioavailability of each drug and could result in varying effectiveness.

Several other classes of medications, including cardiac medications, have shown heterogeneous effects (14). The lipid-lowering agent cerivastatin has been removed from the market because an unusually high proportion of patients experienced rhabdomyolysis (15). Individual calcium-channel blockers have also differed in terms of their beneficial and side effects (16, 17). In fact, researchers have suggested that within the classes of both nitrates (18) and calcium-channel blockers (19), short-acting and long-acting drugs exhibit different properties.

The tendency for physicians to assume a class effect can be seen by the increase in prescriptions for ramipril in patients who have had acute myocardial infarction (20) since the publication of the Heart Outcomes Prevention Evaluation (HOPE) (21). However, the protocol for this trial did not specifically target patients in the period immediately after acute myocardial infarction. In practice, physicians seem to assume that ramipril is indicated for secondary prevention after acute myocardial infarction, even in patients without congestive heart failure (CHF) (22–24). Our study examined the class effect of ACE inhibitors on 1-year mortality when the ACE inhibitors were prescribed to elderly patients immediately after acute myocardial infarction.

METHODS

Study Group and Data Sources

We used the administrative database that stores the information on hospital discharge summaries for the province of Quebec (Maintenance et Exploitation des Données

pour l'Étude de la Clientèle Hospitalière [Med-Echo]) to create a cohort of patients 65 years of age or older who were hospitalized for acute myocardial infarction and were alive at discharge. Patients were identified on the basis of a discharge diagnosis of acute myocardial infarction (International Classification of Diseases, Ninth Revision, code 410) between 1 April 1996 and 31 March 2000. Using encrypted Medicare numbers, we then linked this cohort with the physician and drug claims database for the province of Quebec (the Régie de l'Assurance Maladie du Québec [RAMQ]). This latter database contains information on all outpatient prescriptions for patients 65 years of age or older as well as all inpatient and outpatient diagnostic and therapeutic procedures in Quebec. This database provides survival status for more than 99% of patients (25). We identified a total of 18 453 patients who had had an acute myocardial infarction; 41% were prescribed ACE inhibitors at discharge after the acute myocardial infarction (**Figure 1**).

Demographic, Clinical, and Hospital Characteristics

As many as 15 secondary diagnoses can be included in the hospital discharge summary database; these secondary diagnoses were used to obtain data about patient comorbid conditions at discharge. We also identified the following in-hospital invasive procedures: cardiac catheterization, percutaneous coronary intervention, and coronary artery bypass graft surgery. In addition, cardiac medications that may influence survival after acute myocardial infarction were identified. Finally, we obtained information on the specialty of the treating physician (3 categories [cardiologist, internist, or general practitioner and others]), as well as on the following characteristics of the hospital in which the acute myocardial infarction was treated: availability of cardiac catheterization, annual acute myocardial infarction volume ($\geq$100 or $<$100 acute myocardial infarctions per year), and urban or rural location.

Prescription Groups

We identified patients who filled at least 1 prescription for an ACE inhibitor within 30 days of discharge. This time frame was used to include patients who may not have filled their prescriptions immediately, despite receiving them at discharge. Almost all patients who have an acute myocardial infarction fill their first prescription within 30 days of discharge (26). The patients were categorized into groups according to the ACE inhibitor on their first prescription filled after discharge. Patients who were switched to another ACE inhibitor during the first year after discharge were excluded because switching often indicates worse prognosis (27).

To determine the extent to which patients followed their treatment regimens for each ACE inhibitor, we calculated several measures of treatment adherence. Among patients with discharge prescriptions, we calculated the proportion of patients who also filled at least 1 prescription during the period 275 to 365 days (that is, 9 to 12 months) after discharge. In addition, we calculated persistence of filled prescriptions as the proportion of time for which a patient was covered by prescriptions during the first year after discharge or the proportion of time until death if the patient died earlier. These measures were calculated on the basis of a variable indicating the duration of each filled prescription available in the drug claims database. We also calculated the proportion of patients for whom persistence was 80% or higher.

Context

Do all angiotensin-converting enzyme (ACE) inhibitors similarly improve survival after myocardial infarction?

Contribution

This retrospective study linked hospital and prescription data from 18 453 patients 65 years of age and older who were admitted to 109 Canadian hospitals for myocardial infarction in the late 1990s. Patients who filled prescriptions for ramipril had lower mortality rates within the first year of hospital discharge than did those who filled prescriptions for several other ACE inhibitors, including captopril, enalapril, fosinopril, and quinapril.

Cautions

Although analyses controlled for multiple potential confounders, the authors could not adjust for unmeasured factors that might make the risk for death seem related to a particular ACE inhibitor.

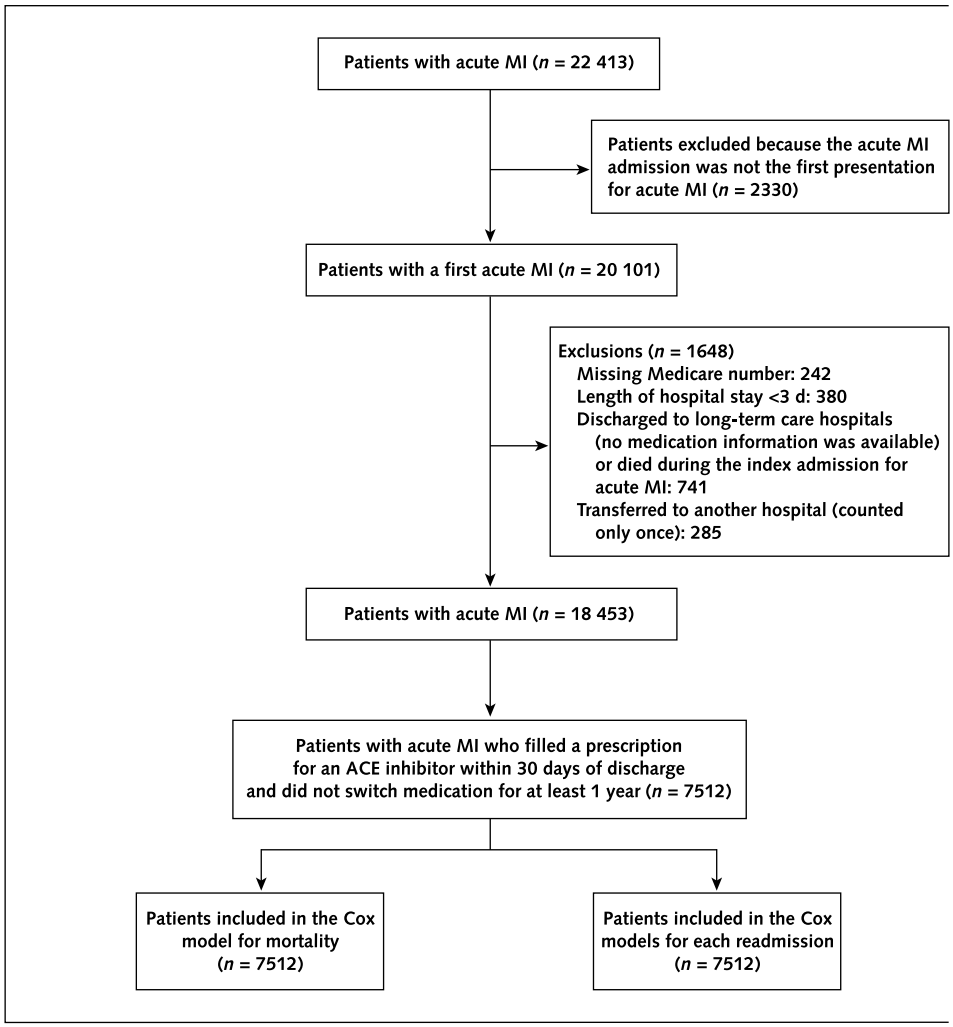
–The Editors

Time-Dependent Covariates

We created 2 time-dependent variables. One indicated periods of exposure and nonexposure for each patient, according to information on dates when subsequent prescriptions were filled and on duration of these prescriptions. The other indicated dosage category (no drug, below target, or at- or above-target). The target dosage of each drug was identified from randomized, controlled trials (26, 28).

Administrative databases do not have a code for missing variables. We assumed that patients with a missing variable for a secondary diagnosis did not have that diagnosis. Validity studies have been performed specifically for the Quebec administrative database and for other similar Canadian databases in general (29). Overall, few data seem to be missing when the databases are validated against chart review, especially for variables that are linked to reimbursement, such as prescriptions and physicians services. The variables for prescriptions include type of drug, dosage category, frequency, and duration. For prescriptions, the variable for dosage was missing for 69 patients (0.9%), and we have attributed the most frequently used dosage of the particular ACE inhibitor to the missing value.

Figure 1. **Flow diagram.**



ACE = angiotensin-converting enzyme; MI = myocardial infarction.

Statistical Analysis

We compared demographic, clinical, physician, and hospital characteristics of patients according to the type of ACE inhibitor prescribed at discharge. Unadjusted mortality throughout 1 year of follow-up for users of each ACE inhibitor was summarized by using Kaplan–Meier curves and compared by using the log-rank test. To account for differences in follow-up and to control for differences among patients' characteristics, a multivariable Cox proportional hazards model (27) was used. In all Cox models, the associations between particular ACE inhibitors and mortality within the first year were adjusted for the following fixed variables: age, sex, CHF, diabetes, cardiac dysrhythmia, cerebrovascular disease, acute renal failure, malignant conditions, shock, in-hospital procedures (cardiac catheterization, percutaneous coronary intervention, coronary artery bypass graft surgery), discharge medications (β-blockers, lipid-lowering agents, nitrates, aspirin, calcium-channel blockers, diuretics, warfarin), the year of acute myocardial infarction to account for temporal trends, physician specialty, and 2 hospital characteristics (availability of cardiac catheterization and acute myocardial infarction volume). Forced-entry regression was used to include these variables in all multivariable models in order to adjust the between-drug comparisons for potential confounders. Because ramipril has increasingly been used in the period immediately after acute myocardial infarction (as a result of the HOPE study) it was a priori selected as a reference category, and adjusted hazard ratios were estimated for the other ACE inhibitors in comparison with ramipril.

The date of 31 March 2001 was used as a censoring point for patients still alive, which enabled us to have 1 year of follow-up information for all patients. As in our mortality analyses, censoring occurs only at this date. Therefore, the assumption of noninformative censoring is completely satisfied because such administrative censoring is, by definition, independent of both patients' characteristics and their future outcomes (30).

The main analyses relied on Cox multivariable models

stratified by the hospital of admission. This accounted for potential confounding by hospital as well as for the possible correlations among outcomes of patients treated in the same hospital. In the preliminary analyses, we tested for possible effect modification of treatment (individual ACE inhibitor vs. ramipril) by hospital volume, physician specialty, and presence of CHF. This was done by adding, in separate models, a set of respective interaction terms between each of these variables and 6 dummy indicators of particular ACE inhibitors. Statistical significance of each set of interaction terms was then tested by using the likelihood ratio test with 6 degrees of freedom; the interactions were removed from the final model if this test failed to reject the null hypothesis at the 0.05 level.

To verify whether the mortality hazard ratios remained constant for the entire groups of patients prescribed different ACE inhibitors at discharge, we tested the proportional hazards hypothesis by using the method of Grambsch and Therneau for all models, not including time-dependent variables (31). Finally, to assess the extent to which the results of between-drug comparisons might be affected by influential observations, we relied on likelihood displacement and influence statistics for the proportional hazards model (32, 33).

In our main analyses, we used a stratified Cox model with fixed covariates indicating which ACE inhibitor was initially prescribed to a given patient. To verify that the potential differences in the exposure time or drug dosage do not affect results of between-drug comparisons, we reanalyzed the data by using a similar multivariable Cox model with 2 additional binary time-dependent variables. One variable indicated current exposure to an ACE inhibitor by assigning a value of 1 to all exposure periods. The other variable assigned the value of 1 to only those periods of exposure when the current dosage was at or above the target dosage and the value of 0 to periods of exposure with a dosage below the target. The inclusion of both time-dependent variables in the same model implied that the former compared the exposure below the target dosage with nonexposure, whereas the latter compared the exposure below target dosage with that at- or above-target dosage.

Finally, to assess the robustness of our findings about potential confounding by indication (as a result of a hypothetical unobserved confounder), we performed sensitivity analyses by using the approach proposed by Greenland (34) and adopted for cohort studies. We considered a hypothetical unobserved risk factor that will be less frequent among ramipril users than among the users of alternative drugs. We then varied assumptions concerning 1) the effect of this confounder on mortality, in terms of hazard ratio and 2) the strength of the confounder association with treatment, in terms of the differences in the prevalence of the confounder across users of different drugs. For each combination of these assumptions, we then calculated how the hazard ratios for individual ACE inhibitors, relative to ramipril, would change after having adjusted for the unobserved confounder.

We used similar multivariable Cox models, stratified by hospital, to estimate the associations between ACE inhibitors prescribed at discharge and readmissions to the hospital resulting from cardiac complications. Because treating death as a censoring event may violate the assumption of noninformative censoring, these analyses were repeated while excluding all patients who died without having the readmission of interest. All statistical analyses were performed by using the SAS (version 8) statistical software package (SAS Institute Inc., Cary, North Carolina) and the S-PLUS 6.0 statistical package (Insightful Corp., Seattle, Washington).

Role of the Funding Source

This study was funded by a grant from the Canadian Institutes of Health Research. The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit this study for publication. The authors had full and unique access to the data for the study.

RESULTS

ACE Inhibitor Prescription Groups

A total of 7512 (41%) of the patients in our study group filled a prescription for an ACE inhibitor within 30 days of discharge and continued to receive this drug for the first year after discharge. Enalapril was most frequently prescribed, accounting for 34% of the prescriptions, followed by lisinopril (29%), fosinopril (12%), ramipril (12%), captopril (6%), quinapril (4%), and perindopril (3%). Overall, patients were followed for an average of 2.3 years since discharge (median, 2.2 years; 25th and 75th percentiles, 1.2 and 3.3 years).

Patient, Physician, and Hospital Characteristics

Table 1 describes the demographic, clinical, physician, and hospital characteristics of patients according to the specific ACE inhibitor prescribed at discharge. The follow-up for ramipril was shorter because use of this drug started later than use of the other ACE inhibitors. Accordingly, patients receiving ramipril tended to undergo more catheterization and percutaneous coronary intervention and to be more commonly prescribed other cardiac medications as a result of secular trends in the use of these procedures and medications.

Prescription Characteristics

For each ACE inhibitor, **Table 2** displays mean values of actual dosages and ramipril-equivalent dosages. The mean dosages prescribed in terms of ramipril equivalent were fairly similar across prescription groups. However, the proportion of patients prescribed an at- or above-target dosage varied from less than 30% for fosinopril and captopril to 88% for lisinopril (**Table 2**).

Mean persistence rates with filled prescriptions over the year after discharge ranged from 70% in the perindo-

Table 1. **Demographic and Clinical Characteristics of Patients with Acute Myocardial Infarction Who Received Prescriptions for Angiotensin-Converting Enzyme Inhibitors***

Characteristic	Ramipril	Enalapril	Lisinopril	Fosinopril	Captopril	Quinapril	Perindopril
Patients, *n*	905	2577	2201	889	421	276	243
Median follow-up (IQR), *d*	493 (406, 723)	866 (488, 1303)	873 (521, 1262)	745 (418, 1130)	991 (410, 1433)	740 (467, 1200)	762 (475, 1138)
Median age, *y*	74	75	75	75	76	75	76
Men, %	58.2	54.5	54.5	55.2	51.8	57.6	49.4
Baseline comorbid conditions, %							
CHF	30.4	39.7	35.6	38.7	44.7	34.8	30.5
Diabetes	26.1	30.5	23.9	33.8	24.9	34.8	24.3
Cardiac dysrhythmia	22.8	24.2	23.1	24.5	28.7	23.6	31.3
Cerebrovascular disease	6.3	8.9	7.7	10.2	9.5	8.3	4.5
Acute renal failure	3.5	5.9	4.1	8.0	6.2	4.0	3.7
Malignant condition	3.8	2.9	2.5	3.4	5.0	2.9	1.2
Shock	1.1	1.5	1.7	1.1	1.4	0.0	1.2
Procedures during initial hospitalization, %							
Catheterization	30.3	24.3	23.1	27.3	16.4	23.2	36.6
PCI	17.5	9.5	12.5	14.4	5.9	9.8	14.4
CABG	2.8	4.4	2.3	3.2	2.6	4.7	4.9
Other prescriptions at discharge, %							
Nitrates	78.8	78.9	79.8	78.3	80.1	73.9	75.7
Aspirin	67.1	65.6	61.6	64.1	67.5	62.7	57.6
β-Blockers	70.8	52.6	56.7	54.3	45.6	55.4	70.0
Lipid-lowering agents	39.2	21.4	30.5	26.9	14.7	31.5	37.0
Calcium-channel blockers	18.3	24.3	25.7	32.2	26.4	29.4	24.7
Diuretics	44.1	57.8	47.2	57.6	65.3	55.1	47.7
Warfarin	21.2	20.5	23.8	19.7	21.9	22.8	29.6
Specialty of treating physician, %							
General practitioner	39.2	48.2	40.1	41.1	58.7	42.4	41.2
Cardiologist	56.8	42.4	44.4	53.4	31.8	49.6	53.5
Internist	4.0	9.4	15.5	5.5	9.5	8.0	5.4
Hospital characteristics, %							
University affiliation	57.9	46.3	38.4	53.1	48.9	51.8	41.2
Catheterization availability	32.8	30.0	18.5	35.9	17.8	24.3	34.2
Low AMI volume†	14.0	14.1	14.2	13.7	13.1	15.9	9.1

* AMI = acute myocardial infarction; CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; IQR = interquartile range (25th, 75th percentiles); PCI = percutaneous coronary intervention.
† Fewer than 100 acute myocardial infarctions per year.

pril and captopril groups to 80% in the quinapril group. The proportion of patients with 80% or higher persistence varied from 56% for captopril to 74% for quinapril. Similarly, in the last 3 months of the first year, the proportion of patients continuing to fill prescriptions ranged from 67% for captopril to 82% for quinapril.

Outcomes after Acute Myocardial Infarction

Figure 2 shows that among patients prescribed an ACE inhibitor at discharge, unadjusted survival was different across exposure groups ($P < 0.001$ for the log-rank test). The left part of **Table 3** summarizes the results of the Cox model, stratified by hospital, with fixed covariates representing drugs prescribed at discharge. After adjustment for potentially confounding patient, physician, hospital, and treatment variables, as well as the year of acute myocardial infarction, patients who initially filled prescriptions for enalapril, fosinopril, captopril, or quinapril had statistically significantly higher 1-year mortality than did patients who filled a prescription for ramipril (**Figure 3**). With ramipril as the reference, adjusted hazard ratios and 95% CIs for mortality within 1 year among the 7512 patients who filled prescriptions for these drugs were 1.47 (CI, 1.14 to 1.89), 1.71 (CI, 1.29 to 2.25), 1.56 (1.13 to 2.15), and 1.58 (CI, 1.10 to 2.28), respectively (**Table 3**). Compared with ramipril, adjusted hazard ratios for patients receiving perindopril and lisinopril were 0.98 (CI, 0.60 to 1.60) and 1.28 (CI, 0.98 to 1.67), respectively.

The right part of **Table 3** summarizes the model with 2 additional time-dependent variables: one accounted for current exposure time and the other accounted for dosage category. Adding the 2 covariates did not materially change the results (**Table 3**). Of note, being at or above the target dosage was not a predictor of mortality (hazard ratio, 0.94 [CI, 0.80 to 1.10]).

Table 2. **Prescription Characteristics for Patients with Acute Myocardial Infarction Who Received Prescriptions for Angiotensin-Converting Enzyme Inhibitor at Discharge***

	Ramipril	Enalapril	Lisinopril	Fosinopril	Captopril	Quinapril	Perindopril
Actual dosage (IQR), *mg*	5 (2.5, 7.5)	10 (5, 10)	10 (5, 10)	12 (10, 10)	50 (25, 75)	20 (10, 20)	4 (2, 4)
Ramipril-equivalent dosage (IQR), *mg*	5 (2.5, 7.5)	5 (2.5, 5.0)	4 (2.5, 5.0)	3 (2.5, 2.5)	3 (2, 5)	4 (2.5, 5)	5 (2.5, 5)
At or above target dosage, %†	62	53	88	22	29	78	61
Persistence of filled prescriptions, %							
Mean persistence‡	75	73	74	75	70	80	70
Patients with high persistence§	66	61	63	64	56	74	56
Prescription filled in the last 3 mo of first year, %‖	75	74	74	76	67	82	69

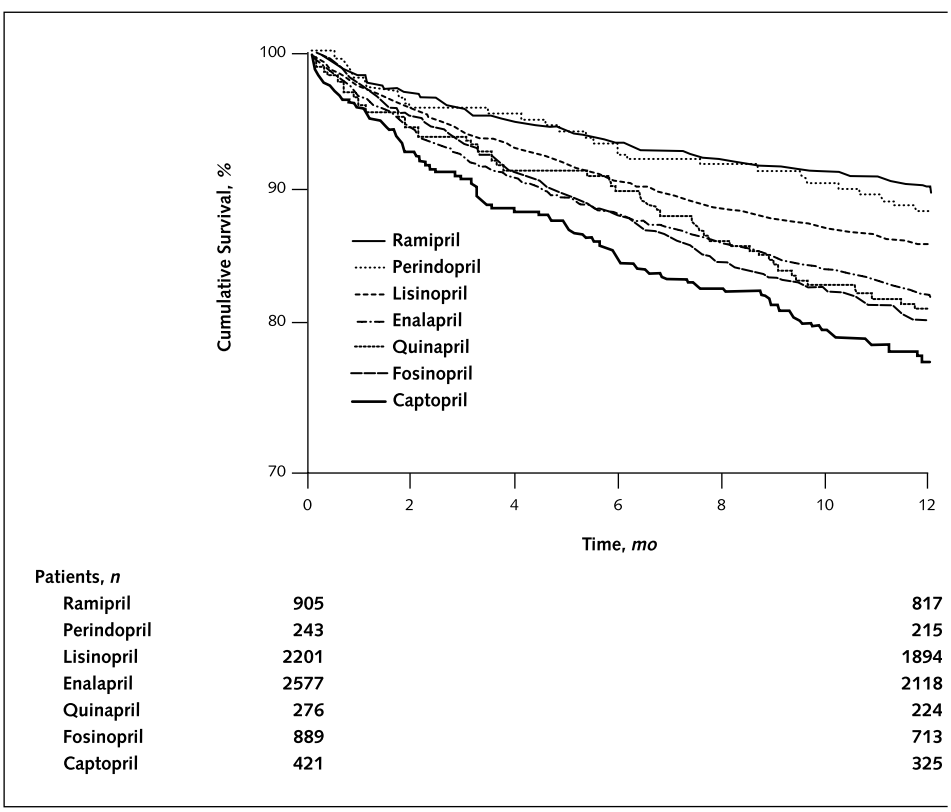
* IQR = interquartile range (25th, 75th percentiles).
† Dosage values are based on each patient's first prescription.
‡ Persistence is defined as the proportion of time for which a patient was covered by prescriptions over the year after discharge or until death if the patient died in the year after discharge.
§ High persistence is defined as having a persistence of 80% or higher.
‖ Proportion of patients who filled at least one prescription during the period 275 to 365 days (i.e., 9 to 12 months) following discharge.

These results are based on a follow-up period truncated at 1 year because exposure information was not available beyond the first year. However, patients had a median follow-up of 2.2 years. When assuming that the same exposure drug and dosage category continued beyond 1 year, the observed differences in mortality across ACE inhibitors persisted up to 5 years of follow-up, and the hazard ratios and 95% CIs were similar (data not shown).

Table 4 shows the results for readmissions due to cardiac complications; we obtained these results after making adjustments similar to those in the fixed model. Enalapril and fosinopril were associated with higher readmission rates for CHF. Readmissions for unstable angina and recurrent myocardial infarction were similar across all prescription groups.

Several additional analyses were performed to test the robustness of these findings. Tests for possible effect modifications of treatment by hospital volume, physician specialty, or the presence of CHF did not reveal any statistically significant interactions ($P > 0.12$ for all interaction

Figure 2. **Unadjusted Kaplan–Meier curves according to angiotensin-converting enzyme inhibitor prescribed within 30 days of discharge.**



$P < 0.001$ for the log-rank test.

Table 3. **Fixed and Time-Dependent Multivariable Cox Model for 1-Year Mortality***

Variable†	Fixed Model‡: Hazard Ratio (95% CI)	Time-Dependent Model: Hazard Ratio (95% CI)
Prescriptions filled		
Ramipril (reference)	–	–
Enalapril	1.47 (1.14–1.89)	1.40 (1.10–1.78)
Lisinopril	1.28 (0.98–1.67)	1.26 (0.98–1.61)
Fosinopril	1.71 (1.29–2.25)	1.61 (1.23–2.10)
Captopril	1.56 (1.13–2.15)	1.40 (1.03–1.91)
Quinapril	1.58 (1.10–2.28)	1.68 (1.18–2.38)
Perindopril	0.98 (0.60–1.60)	1.11 (0.73–1.71)
Other cardiac prescriptions filled		
Nitrates	0.93 (0.80–1.08)	0.95 (0.82–1.11)
Aspirin	0.92 (0.80–1.05)	0.90 (0.79–1.02)
β-Blocker	0.72 (0.64–0.82)	0.73 (0.65–0.83)
Lipid-lowering agents	0.76 (0.64–0.90)	0.75 (0.64–0.88)
Calcium-channel blockers	1.12 (0.99–1.28)	1.11 (0.98–1.26)
Diuretics	2.02 (1.75–2.35)	2.14 (1.85–2.48)
Warfarin	0.88 (0.74–1.03)	0.88 (0.75–1.03)
Comorbid factors		
Age/years	1.03 (1.02–1.04)	1.03 (1.02–1.04)
Sex	1.08 (0.96–1.21)	1.10 (0.98–1.23)
Congestive heart failure	1.39 (1.23–1.58)	1.36 (1.21–1.54)
Diabetes	1.38 (1.22–1.56)	1.43 (1.26–1.61)
Cerebrovascular disease	1.40 (1.18–1.67)	1.45 (1.23–1.73)
Malignant conditions	2.94 (2.35–3.68)	2.78 (2.24–3.45)
Cardiac dysrhythmias	1.11 (0.97–1.27)	1.09 (0.96–1.24)
Renal failure	1.25 (1.02–1.54)	1.23 (1.00–1.50)
Shock	1.13 (0.74–1.75)	1.12 (0.73–1.71)
Procedures during index admission		
Catheterization	0.76 (0.60–0.95)	0.77 (0.61–0.96)
PCI	0.60 (0.42–0.86)	0.63 (0.44–0.89)
CABG	0.20 (0.09–0.45)	0.18 (0.08–0.42)
Hospital volume§	0.73 (0.34–1.57)	0.80 (0.66–0.96)
Availability of catheterization laboratory‖	–	0.91 (0.78–1.07)
Treating physician¶		
Cardiologist	0.89 (0.68–1.16)	0.96 (0.83–1.11)
Internist	0.96 (0.68–1.35)	1.07 (0.88–1.30)
Time-dependent variables		
Period exposed	–	0.37 (0.31–0.43)
At- or above-target dosage	–	0.94 (0.80–1.10)

* CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.
† An additional variable that was not statistically significant was year of admission for acute myocardial infarction.
‡ Analyses are stratified by hospital.
§ High-volume hospital (≥100 acute myocardial infarction admissions per year) is the reference category.
‖ Availability of catheterization laboratory is not shown in the fixed model because the fixed model was stratified by hospital.
¶ General practitioner is the reference category.

terms). The proportional hazards hypothesis was not rejected with respect to the individual drugs compared with ramipril (data not shown). Finally, we performed sensitivity analyses to assess the magnitude of hidden bias necessary to materially alter the conclusion that patients prescribed ramipril had lower mortality than patients prescribed other ACE inhibitors (34). These analyses showed that the findings were sensitive to a combination of an unobserved confounder with a hazard ratio of at least 2 and a strong imbalance of that confounder across groups (for example, present in 80% of users of the other drugs compared with only 40% of the users of ramipril or 70% vs. 30% or 90% vs. 50%).

DISCUSSION

Our study suggests that ACE inhibitors do not lead to a similar reduction in mortality in the first year after acute myocardial infarction. We showed that at currently used dosages, enalapril, captopril, fosinopril, quinapril, and lisinopril were all associated with higher mortality than was ramipril in the first year after acute myocardial infarction. The comparisons for lisinopril and ramipril were not statistically significant. Patients who filled prescriptions for perindopril did not have a statistically significant different mortality from users of ramipril.

Although ACE inhibitors share the same basic struc-

ture, there are important structural and pharmacologic differences within the class (35) (**Table 5**). These characteristics influence the potency and bioavailability of the drug and may explain some of the variation in effectiveness that we observed. Each ACE inhibitor has a functional group that binds to the target ACE by forming a zinc ligand (36). This functional group forms the main structural difference between drugs; the carboxyl group is most common, followed by the sulfhydryl group and the phosphinyl group (37). The carboxyl-containing ACE inhibitor group has been shown to have the highest potency (38). Although ramipril is a carboxyl-containing ACE inhibitor, enalapril and quinapril are also members of this group, and, in the current study, these drugs were associated with higher mortality than was ramipril. Furthermore, some of the adverse effects exerted by ACE inhibitors were reported to be more frequently associated with members of the sulfhydryl-containing group (36). Captopril, which was associated with higher mortality in our analyses, is the only drug in this group. The lipophilicity of a drug is an important pharmacologic property that determines the level of tissue penetration (13), and the effect of an ACE inhibitor may depend on the extent to which tissue penetration occurs (37). Despite this evidence, we could find no systematic differences in mortality among drugs with high and low lipophilicity.

Figure 3. **Adjusted hazard ratios and 95% CIs for mortality within 1 year of acute myocardial infarction (*MI*) according to angiotensin-converting enzyme inhibitor prescribed.**

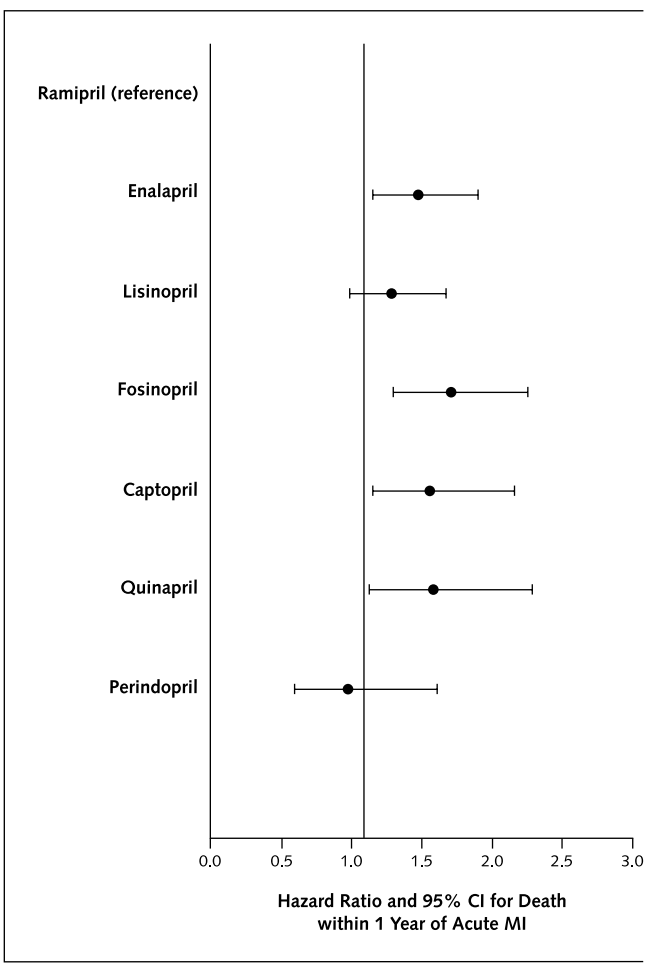


Table 4. **Adjusted Hazard Ratios and 95% CIs for 1-Year Readmissions Due to Cardiac Complications***

Cardiac Complication	Hazard Ratio (95% CI)
Congestive heart failure (*n* = 7443)	
Ramipril (reference)	–
Enalapril	1.44 (1.03–2.01)
Lisinopril	1.29 (0.91–1.82)
Fosinopril	1.83 (1.27–2.62)
Captopril	1.16 (0.75–1.81)
Quinapril	1.42 (0.88–2.29)
Perindopril	0.44 (0.18–1.08)
Unstable angina (*n* = 7469)	
Ramipril (reference)	–
Enalapril	1.16 (0.87–1.55)
Lisinopril	1.06 (0.79–1.42)
Fosinopril	0.78 (0.55–1.10)
Captopril	1.01 (0.67–1.52)
Quinapril	1.14 (0.74–1.78)
Perindopril	1.22 (0.71–2.10)
Recurrent myocardial infarction (*n* = 7482)	
Ramipril (reference)	–
Enalapril	1.30 (0.87–1.96)
Lisinopril	1.39 (0.92–2.12)
Fosinopril	1.19 (0.74–1.91)
Captopril	0.97 (0.54–1.75)
Quinapril	0.98 (0.51–1.89)
Perindopril	1.83 (0.87–3.84)

* Patients were excluded if their readmission occurred before the first prescription. These are models that include the same fixed covariates as models for mortality (left part of Table 3); they were stratified by hospital.

Several ACE inhibitors that we studied have been shown to be better than placebo in randomized, controlled trials (39, 40) (**Table 6**). However, most trials have studied only 1 ACE inhibitor against placebo. Captopril, enalapril, lisinopril, ramipril, and fosinopril have been studied extensively; many trials have confirmed that they reduce mortality after acute myocardial infarction (39) in patients with CHF or low left ventricular ejection fraction. Conversely, randomized trials of quinapril (41, 42) and perindopril (43) did not include patients who had had an acute myocardial infarction.

Although our study has many limitations because of its observational nature, we believe that it is the first study to evaluate the long-term effects of 7 different ACE inhibitors in a head-to-head comparison. Other smaller studies have performed head-to-head comparisons of 2 specific ACE inhibitors at most. In the Placebo-Controlled Randomized ACE Inhibitor Comparative Trial in Cardiac Infarction and Left Ventricular Function (2), either captopril or enalapril was administered to patients with acute myocardial infarction and low ventricular function. Even though effects on left ventricular function were similar, patients in

Table 5. **Pharmacologic Characteristics of the Angiotensin-Converting Enzyme Inhibitors Studied**

Drug*	Binding Group	Prodrug	Lipophilicity†	Half-Life, *h*	Route of Elimination
Enalapril (1994)	Carboxyl	Yes	++	11.0	Renal
Captopril (1986)	Sulfhydryl	No	+	2.0	Renal
Fosinopril (1993)	Phosphinyl	Yes	+++	12.0	50% renal, 50% hepatic
Lisinopril (1991)	Carboxyl	No	0	13.0	Renal
Perindopril (1995)	Carboxyl	Yes	+	9.0	Renal
Quinapril (1992)	Carboxyl	Yes	++	3.0	Renal
Ramipril (1994)	Carboxyl	Yes	+	12.0	70% renal, 30% hepatic

* Years in parentheses represent the year in which the drug was added to the Quebec formulary. The order of the list is not by preferred usage for the treatment of acute myocardial infarction.
† 0 = no lipophilicity; + = mild lipophilicity; ++ = moderate lipophilicity; +++ = greatest lipophilicity.

the enalapril group had substantially lower 90-day and 1-year mortality rates. In our study, mortality associated with enalapril was only marginally lower than mortality associated with captopril, and this difference disappeared after we adjusted for exposure periods (**Table 3**). Moreover, in the Cooperative New Scandinavian Enalapril Survival Study II (44), enalapril had no beneficial effect on survival when compared with placebo. In separate trials, captopril had effects similar to those of quinapril (45) and lisinopril (46). However, these trials studied patients with CHF rather than acute myocardial infarction.

Our study has several limitations. First, the administrative database did not contain detailed clinical information. As with all observational studies (47), hidden biases or inability to account for all factors related to both physicians' prescription choices and patients' risk for death might be responsible for the observed differences across ACE inhibitors. To limit the possibility of biases, we restricted the study group to patients who did not switch to another ACE inhibitor for the first year after discharge. We also adjusted for multiple potentially confounding variables, including CHF, and found that interactions between treatment and CHF were not statistically significant. Differences among individual drugs remained similar in patients with CHF. Nevertheless, we cannot exclude with certainty the possibility that physicians may still have selectively prescribed certain ACE inhibitors to sicker patients. In sensitivity analyses, we explored the amount of hidden bias from an unmeasured confounder necessary to materially alter the conclusion that patients prescribed ramipril had lower mortality than did patients prescribed other ACE inhibitors. We found that an unmeasured confounder with a hazard ratio of at least 2 and a strong imbalance across groups (for example, present in 80% of the users of the other drugs compared with only 40% of the users of ramipril) might overturn conclusions.

Second, our database provides no information on in-hospital medications. Many randomized trials that have shown the beneficial effects of ACE inhibitors involved therapy that was initiated within 36 hours of acute myocardial infarction (12, 39). We could not account for such early prescriptions. However, most patients fill their prescription on the day of discharge, and, if this is not possible, patients are given a 24-hour supply on hospital discharge. The ACE inhibitor prescribed on discharge has usually been started while the patient is in the hospital.

Third, as in most database pharmacoepidemiologic studies (48), exposure time to ACE inhibitors was measured by filled prescriptions, which may not faithfully measure pill intake. Dosage measurement was imprecise and was categorized grossly according to "target dosage." Even in a group of patients who have just sustained a life-threatening medical event, filled prescriptions may not correspond to the particular ACE inhibitor taken or the period

Table 6. **Overall Mortality among Randomized, Controlled Trials Studying the Administration of Angiotensin-Converting Enzyme Inhibitors***

Study (Reference)	Drug	Patients, *n*	Length of Follow-up	Mortality Rate, %		*P* Value
				Treatment	Placebo	
ISIS-4 (5)	Captopril	58 050	1 mo	7.2	7.7	0.01
GISSI-3 (3)	Lisinopril	19 394	6 wk	9.1	9.6	0.01
CCS-1 (4)	Captopril	13 634	1 mo	9.1	9.6	0.15
CONSENSUS-II (44)	Enalapril	6090	6 mo	11.0	10.2	>0.2
HOPE (20)†	Ramipril	4892	5 y	16.3‡	20.9‡	<0.01
SAVE (6)	Captopril	2231	1 y	10.3	11.6	0.02
AIRE (1)	Ramipril	1986	1 y	15.0	19.0	0.002

* AIRE = Acute Infarction Ramipril Efficacy study; CCS = Chinese Cardiac Study; CONSENSUS II = Cooperative New Scandinavian Enalapril Survival Study II; GISSI-3 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-3; HOPE = Heart Outcomes Prevention Evaluation; ISIS-4 = Fourth International Study of Infarct Survival; SAVE = Survival and Ventricular Enlargement trial. Only trials with ≥1986 participants are included.
† Only study patients with a history of acute myocardial infarction are included in these data.
‡ Composite outcome of death, myocardial infarction, or stroke.

during which it is taken. However, prescription duration was 30 days for most patients and did not vary across ACE inhibitors. Furthermore, interruptions between prescriptions were short (median, 3 days). It is unlikely that the interruption in timing and its effect on mortality would vary from one drug to the other. Indeed, the time-dependent analyses that account for the interruptions (right part of **Table 3**) yield very similar results for between-drug comparisons with the model with fixed treatment groups (left part of **Table 3**); this finding indicates that interruptions in drug use have a minimal effect.

Fourth, such administrative databases do not distinguish between missing diagnoses for comorbid conditions and absent diagnoses. This could lead to nondifferential misclassification, which might reduce the estimated effects of comorbid conditions. Overall, few data seem to be missing when the databases are validated against chart review, especially for variables, such as prescriptions and physician services, that are linked to reimbursement (29). For 69 patients (0.9% of the sample) who had a missing dosage, we simply assigned the mean dosage of a given ACE inhibitor. This ignored uncertainties of these missing values but had only minimal effect because the proportion of missing dosages was extremely small.

Finally, the follow-up for patients prescribed ramipril was shorter because this ACE inhibitor was the last one to have been added to the formulary for use after acute myocardial infarction. Yet, in survival analytic models, such as Cox regression, patients contribute to the analysis only over the time period corresponding to their individual duration of follow-up. Thus, the outcomes for patients using ramipril are compared with those of the users of other drugs only over the period when the patients are at risk. This avoids any systematic length bias resulting from differences in duration of follow-up. However, the proportional hazards assumption implying that relative risks are constant over time must be satisfied (49), as it was in our study.

In summary, our results suggest that not all drugs within the class of ACE inhibitors should be considered to have the same effect. We have shown that, at currently used dosages, elderly patients who filled prescriptions for ramipril had statistically significant lower mortality within the first year after acute myocardial infarction than did users of several other ACE inhibitors. The exact mechanisms causing these differences are unclear, although they are probably related to the structural and pharmacologic characteristics of the individual drugs. As we provide care for patients who have had an acute myocardial infarction, physicians who are choosing an ACE inhibitor when indicated should not assume a class effect. Given that this study is a retrospective, observational study of administrative databases, large randomized clinical trials or prospective clinical studies should confirm these results.

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