Reduced Mortality Associated With the Use of ACE Inhibitors in Patients With Type 2 Diabetes

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OBJECTIVE — ACE inhibitor therapy is widely used in lower-risk patients with type 2 diabetes to reduce mortality, despite limited evidence to support this clinical strategy. The aim of this study was to evaluate the association between ACE inhibitor use and mortality in patients with diabetes and no cardiovascular disease.

RESEARCH DESIGN AND SETTINGS — Using the Saskatchewan health databases, 12,272 new users of oral hypoglycemic agents were identified between the years of 1991 and 1996. We excluded 3,202 subjects with previous cardiovascular disease. Of the remaining subjects, 1,187 "new users" of ACE inhibitors were identified (ACE inhibitor cohort). Subjects not receiving ACE inhibitor therapy throughout the follow-up period served as the control cohort ($n = 4,989$). Subjects were prospectively followed until death or the end of 1999. Multivariate Cox proportional hazards models were used to assess differences in all-cause and cardiovascular-related mortality between cohort groups.

RESULTS — Subjects were 60.7 ± 13.7 years old, 43.6% female, and were followed for an average of 5.3 ± 2.1 years. Mean duration of ACE inhibitor therapy was 3.6 ± 1.8 years. We observed significantly fewer deaths in the ACE inhibitor group (102 [8.6%]) compared with the control cohort (853 [17.1%]), with an adjusted hazard ratio (HR) and 95% CI of 0.49 (0.40–0.61) ($P < 0.001$). Cardiovascular-related mortality was also reduced (40 [3.4%] vs. 261 [5.2%], adjusted HR, 0.63 [0.44–0.90]; $P = 0.012$).

CONCLUSIONS — The use of ACE inhibitors was associated with a significant reduction in all-cause and cardiovascular-related mortality in a broad spectrum of patients with type 2 diabetes and no cardiovascular disease.

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M ortality in individuals with type 2 diabetes is mainly attributed to the macrovascular complications of cardiovascular and cerebrovascular disease (1,2). Although aggressive management of hypertension, lipids, smoking cessation, and blood glucose are emphasized in recent guidelines, these traditional risk factors do not fully account for the higher prevalence and severity of cardiovascular disease in individuals with type 2 diabetes (3,4). As a result, novel risk factors, such as activation of the renin-angiotensin-aldosterone system, are being examined (5). Evidence from large-scale clinical trials has suggested that attenuation of the renin-angiotensin-aldosterone system by ACE inhibitors may reduce cardiovascular morbidity and mortality in patients with established cardiovascular disease (5–8).

There have been, to our knowledge, no studies designed to directly evaluate the effects of ACE inhibitors on cardiovascular disease in patients with diabetes. Thus, the evidence available to guide clinical decision making is based on subgroup analyses of larger trials (7,8). For example, the Heart Outcomes Prevention Evaluation (HOPE) study (8) was designed to study the effects of the ACE inhibitor, ramipril, in 9,297 high-risk individuals (38% with diabetes). Over a median follow-up of 4.5 years, patients who received ramipril had a 22% reduction in the primary outcome of myocardial infarction, stroke, or death from cardiovascular causes. In addition, there were 26 and 16% reductions in cardiovascular-related death and death from any cause, respectively, in favor of the ramipril group. Although HOPE provided clear evidence of the benefits of ACE inhibitors, it is important to note that only 20% of individuals enrolled were clinically free of cardiovascular disease at baseline. A subgroup analysis of these 1,135 patients (99% with diabetes) did not show a beneficial effect of treatment with ramipril, although this particular subgroup analysis was both post hoc and underpowered (8,9). Similar results, limited to subgroup analyses, have also been shown (7) in other higher-risk populations exposed to ACE inhibitors.

Currently, ACE inhibitor therapy is widely used for patients with type 2 diabetes, including those at lower risk, despite limited evidence to support this clinical strategy. Therefore, it is unlikely that a randomized, placebo-controlled trial with ACE inhibitors will be con-

ducted in this population. Accordingly, we conducted a large, population-based, observational study to test the hypothesis that ACE inhibitor use would be associated with reduced all-cause and cardiovascular-related mortality in a broad range of patients with type 2 diabetes without clinical cardiovascular disease.

RESEARCH DESIGN AND METHODS

Subjects eligible for inclusion into our study cohorts were registered beneficiaries of Saskatchewan Health between 1 January 1991 and 31 December 1996, aged ≥30 years, and had at least 1 year of continuous coverage in the provincial health insurance plan.

The Saskatchewan Health insurance plan provides universal health coverage for essentially all residents (~1 million people) in the Province of Saskatchewan. Approximately 9% of the population is not eligible for prescription drug benefits through Saskatchewan Health. Most notably, this includes federal employees (e.g., Royal Canadian Mounted Police), federal inmates, and Registered Indians (10).

From this pool of potential subjects, we identified 12,272 first-time users of oral hypoglycemic agents based on prescription claims for a sulfonylurea or metformin (hereafter referred to as newly treated patients with diabetes) (11). We then categorized this population with newly treated diabetes according to their use of ACE inhibitors: 6,557 (53.4%) subjects were classified into the new ACE inhibitor user cohort based on prescription claims for ACE inhibitors from 1 January 1991 through 31 December 1999 or into our control cohort of ACE inhibitor nonusers (*n* = 5,715; 46.6% of sample).

To control for baseline risk of cardiovascular disease before the diagnosis of diabetes or initiation of ACE inhibitor therapy, we excluded subjects (*n* = 3,202) with established cardiovascular diagnoses based on either a 3-year prior hospital separation history for cardiovascular disease (online appendix [available at http://care.diabetesjournals.org]) or prescription claims directed at symptomatic coronary heart disease (nitrates) or congestive heart failure (loop diuretics) (12–15). Individuals exposed to ACE inhibitors before the initiation of their oral hypoglycemic agents were also excluded (*n* = 1,559). Finally, 1,335 (10.9%) subjects were excluded due to insufficient exposure to an ACE inhibitor (<1 year, according to our a priori definitions). Thus, our final analysis included 6,176 subjects, 1,187 patients in the ACE inhibitor cohort and 4,989 in the control cohort.

Sociodemographic data and a modified comorbidity index, the Chronic Disease Score (CDS), were also collected. The CDS provides an indication of the burden of concurrent comorbidities by identifying specific drug therapies during the follow-up period (16–18). The CDS is well validated, and higher scores are associated with increased mortality, hospitalization rates, and health resource utilization (16–18). A modified CDS was used in this analysis, which was updated to include a wider range of marker drugs than originally identified and has been previously utilized with this dataset (11).

Outcomes

Our primary study outcomes were all-cause and cardiovascular-related mortality. Health services data for the cohorts were followed prospectively for identification and classification of clinical events from the study index date until death, departure from the province, or 31 December 1999. The underlying cause of death was documented by trained coders who applied World Health Organization (WHO) standardized decision rules. Specific ICD-9 codes for cardiovascular-related mortality were identified (online appendix).

Analysis

Using Cox proportional hazards regression models, crude and adjusted hazard ratios (HRs) and 95% CIs were calculated to assess the relationship between ACE inhibitor use and outcomes. Potential confounding variables included in the multivariate model included age, sex, a modified CDS, insulin therapy, and other drug therapies known to affect cardiovascular outcomes (i.e., lipid-lowering drugs, β-blockers, calcium channel blockers, antiplatelet agents, diuretics, antiarrhythmics, metformin, and nitroglycerin). In addition, all potentially clinically important first-order interactions were assessed in the Cox proportional hazards model; no important or statistically significant ($P < 0.10$) interactions were identified.

In addition, to adjust for potential selection bias, we calculated a propensity score intended to represent the likelihood of receiving one of the treatments given the individual's characteristics and included this as a covariate in the primary multivariate models (19–21). The inclusion of the propensity score in the analysis, however, made no significant difference in the point estimates obtained (i.e., <2% change in point estimates) or our conclusions; thus, only the simpler primary multivariate models are presented here.

RESULTS — The mean (±SD) age for all subjects was 60.7 ± 13.7 years and 56.4% were men (Table 1). The mean (±SD) duration of follow-up was 5.3 ± 2.1 years, for a total of >32,000 patient-years. The ACE inhibitor cohort was somewhat younger, contained fewer men, had a longer duration of follow-up, greater comorbidities, and significantly more prescription claims for cardiovascular- and diabetes-related medications compared with the control group (Table 1). The mean duration of exposure to ACE inhibitor therapy was 3.6 ± 1.9 years (range 1.0–8.8).

There were 853 (17.1%) deaths in the control group compared with 102 (8.6%) in the ACE inhibitor group ($P < 0.001$). Of these, 261 (5.2%) cardiovascular-related deaths occurred in the control group and 40 (3.4%) in the ACE inhibitor group ($P = 0.007$). The unadjusted HR (95% CI) for all-cause and cardiovascular-related mortality were 0.43 (0.35–0.52, $P < 0.001$) and 0.54 (0.39–0.76, $P < 0.001$), respectively (Table 2).

The adjusted HRs (95% CI), after controlling for age, sex, CDS, and drug therapies known to affect cardiovascular outcomes, were 0.49 (0.40–0.61, $P < 0.001$) for all-cause and 0.63 (0.44–0.90, $P = 0.012$) for cardiovascular-related mortality (Table 2). The adjusted survival curves for all-cause and cardiovascular-related mortality appeared similar, separating early and continuing to diverge throughout the follow-up period (Fig. 1).

CONCLUSIONS — Our results suggest that the use of ACE inhibitor therapy in a broad spectrum of patients with newly treated type 2 diabetes is associated with a reduction in all-cause and cardiovascular-related mortality. After adjusting for important clinical variables, we observed a 51% reduction in all-cause mortality and a 23% reduction in cardio-

Table 1 —*Characteristics of 6,176 newly treated patients with type 2 diabetes*

Characteristic	Control cohort	ACE inhibitor cohort	P
n	4,989	1,187	—
Age (years)	60.9 ± 14.0	59.8 ± 12.2	0.013
Men	2,903 (58.2)	580 (48.9)	<0.001
Duration of follow-up (years)	5.1 (2.2)	6.0 (1.7)	<0.001
Median	5.1	6.0	
CDS	5.8 ± 3.6	9.2 ± 3.0	<0.001
Median	5.0	9.0	
Medications*			
Antiplatelet therapy	475 (9.5)	180 (15.2)	<0.001
Antiarrhythmic agent	271 (5.4)	96 (8.1)	0.001
β-Blockers	560 (11.2)	310 (26.1)	<0.001
Calcium channel blockers	546 (10.9)	374 (31.5)	<0.001
Other diuretics	344 (6.9)	356 (30.0)	<0.001
Loop diuretics	561 (11.2)	207 (17.4)	<0.001
Lipid-lowering therapy	617 (12.4)	267 (22.5)	<0.001
Nitroglycerin	428 (8.6)	142 (12.0)	<0.001
Metformin	2,752 (54.5)	862 (72.6)	<0.001
Insulin	586 (11.7)	157 (13.2)	0.159

Data are means ± SD or n (%). *Categories are not mutually exclusive.

vascular-related mortality. In absolute terms, we estimate that 12 newly treated patients with type 2 diabetes would need to be treated with an ACE inhibitor for about 4 years to prevent one death.

These results are generally consistent with those observed in other studies (22–24) evaluating ACE inhibitor therapy in people with diabetes. Direct comparison with other trials is difficult, however, due to different study methods, comparative treatments under study, patient populations, and clinical outcomes assessed. Of the studies completed to date, the HOPE study most closely resembles the patient population and outcomes of interest in our analysis. In the main HOPE study (8), ramipril significantly lowered the risk of all-cause and cardiovascular-related death. In the participants of HOPE who had diabetes (n = 3,577 [38%]), there was a 24 and 37% relative risk reduction in all-cause and cardiovascular-related mortality, respectively, for patients who received ramipril (9). Subgroup analysis of those patients without cardiovascular disease at baseline (n = 1,119) showed no significant benefit of ramipril. In contrast, our study suggests that ACE inhibitors are associated with significant mortality benefits in the lower-risk subgroup of patients with type 2 diabetes and no clinical cardiovascular disease.

The strengths of our study include the inclusiveness of the population (i.e., a broad population of people with diabetes), the comprehensiveness of the database, and the long and consistent duration of follow-up. The Saskatchewan Health databases have been used in numerous epidemiological studies (11,25–27) evaluating outcomes with drug use and are considered to be comprehensive and of high quality. Nevertheless, given the observational nature of the analyses, several alternative explanations are possible. We did not have access to clinical information regarding the baseline cardiovascular risk and modifiable cardiovascular risk factors of the subjects (e.g., glycemic control, hypertension, lipids, renal function, smoking, and BMI). It is possible that subjects in the ACE inhibitor group had a lower baseline risk for all-cause and cardiovascular-related mortality. Control for these factors was possible to a certain extent by examining only newly treated subjects with diabetes and excluding all subjects who had a history of cardiovascular disease or had a prescription claim for a product containing nitroglycerin or a loop diuretic. Furthermore, we adjusted all analyses for a well-validated measure of comorbidity (16–18). Finally, we observed that subjects in the ACE inhibitor cohort used more cardiovascular-related medications compared with the control cohort. We have interpreted this to mean that they may have had a greater burden of cardiovascular disease and, therefore, increased overall cardiovascular risk. If this were the case, in the absence of a true ACE inhibitor benefit, we might have observed an increased risk of mortality in the ACE inhibitor cohort. Our interpretation of an increased cardiovascular risk in the ACE inhibitor cohort is supported by the observed greater use of nitrates, a symptomatic treatment, which was independently associated with an increased risk of cardiovascular events.

We also attempted to control for comorbidities unrelated to diabetes and cardiovascular disease by including the modified CDS in the multivariate analysis. Again, patients in the ACE inhibitor group had greater comorbidities and would have been expected to have a greater risk of mortality. We acknowledge that not all comorbidities would be captured with the use of the CDS; however, a significant proportion of the major comorbidities that affect patient outcomes was captured (16–18).

There are limitations inherent to all administrative data. Since exposure status was based on prescription dispensing records, there is no method to ensure that subjects were adherent with their medications. All subjects in the ACE inhibitor group had to have received ACE inhibitors for a minimum of 1 year and, on average, for almost 4 years. It is unlikely

Table 2 —*Mortality rates in patients with type 2 diabetes according to ACE inhibitor exposure*

	Cohort		HR	
Outcome	Control	ACE inhibitor	Crude	Adjusted
n	4,989	1,187	—	—
All-cause mortality	853 (17.1)	102 (8.6)*	0.43 (0.35–0.52)	0.49 (0.40–0.61)
Cardiovascular-related mortality	261 (5.2)	40 (3.4)†	0.54 (0.39–0.76)	0.63 (0.44–0.90)

Data are n (%) or HR (95% CI). *P < 0.001; †P = 0.007.
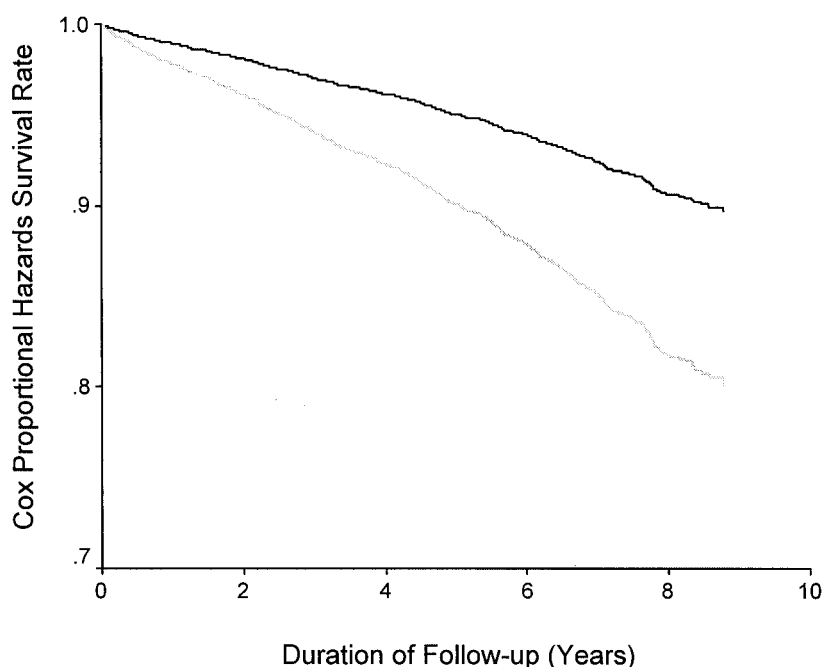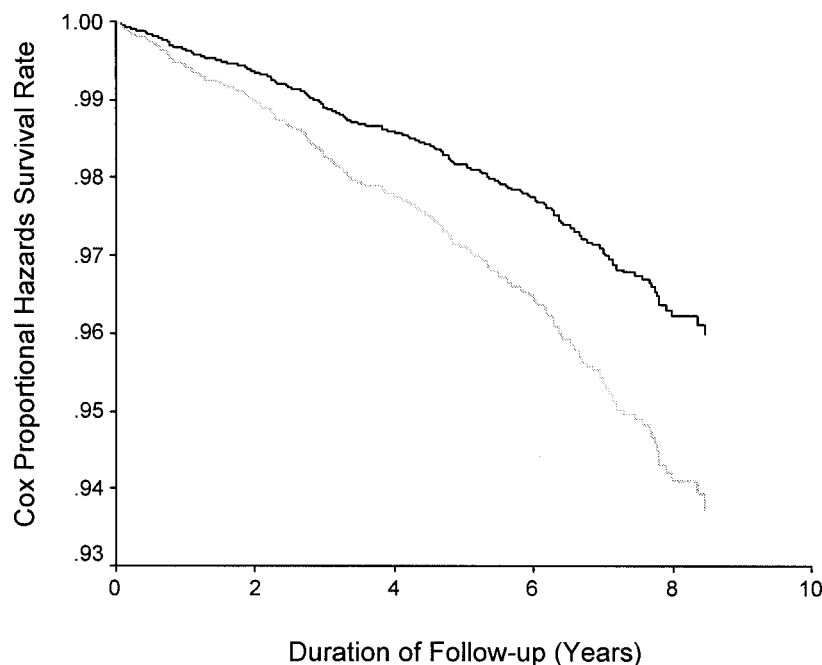
A All-Cause Mortality

B Cardiovascular-Related Mortality

Figure 1—*Adjusted Kaplan-Meier survival curves for clinical outcomes in patients with type 2 diabetes, stratified by ACE inhibitor exposure. A: All-cause mortality. B: Cardiovascular-related mortality. Black line, ACE inhibitor cohort; gray line, control cohort.*

mortality. As it is unlikely that a randomized controlled trial of ACE inhibitor verses placebo therapy in patients with diabetes will ever be undertaken, our observational data may provide the best available evidence that many patients with diabetes will derive substantial mortality benefits from the routine use of ACE inhibitors.

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subjects would continue to refill and bear the expense burden associated with these prescriptions if they were not taking the medication.

Our study suggests that ACE inhibitors can be used by many newly treated patients with type 2 diabetes and that this practice may be associated with reduced

dopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 362:782–788, 2003

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