The striking effect of the Heart Outcomes Prevention Evaluation (HOPE) on ramipril prescribing in Ontario

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Abstract

Background: The Heart Outcomes Prevention Evaluation (HOPE), a Canadian-led, multicentre, randomized controlled trial, demonstrated the effectiveness of the ACE inhibitor ramipril in the secondary prevention of cardiovascular disease in patients who were at high risk for cardiovascular events but did not have left ventricular dysfunction or heart failure. We studied whether HOPE affected the prescribing of ACE inhibitors generally, and ramipril specifically, in Ontario, where the trial was coordinated.

Methods: We used linked administrative databases to examine prescribing patterns for ACE inhibitors in the 1.29 million to 1.54 million elderly (aged 66 and over) residents of Ontario during the study period and specifically those with diabetes or congestive heart failure. For all new prescriptions for these drugs filled between Jan. 1, 1993, and Mar. 31, 2001, we conducted time-series analyses to measure any association with the release of the HOPE results.

Results: The monthly number of new prescriptions for ramipril from the time it was introduced in 1995 until HOPE's early termination, in April 1999, peaked at 58 per 100 000 elderly Ontario residents. The rate increased to 92/100 000 in May, coincident with newspaper coverage of the trial's early termination, then fell back to 63/100 000 in August. After HOPE's results were formally released, starting Aug. 31, the rate increased significantly; it peaked at 304/100 000 in May 2000 ($p < 0.01$). The market share of ramipril among ACE inhibitors also increased significantly ($p < 0.01$), both overall and among patients with diabetes or congestive heart failure.

Interpretation: HOPE led to a striking and unprecedented increase, over 400%, in ramipril prescribing to elderly Ontario residents, including those not eligible for the trial. Many physicians are now prescribing ramipril for patients with diabetes or congestive heart failure.

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The benefits of angiotensin-converting-enzyme (ACE) inhibitors have been well established in the treatment of patients with congestive heart failure,[1,2] acute myocardial infarction,[3] diabetes mellitus,[4] non-diabetic renal disease[5] or hypertension.[6] Although it is controversial whether ACE inhibitors are interchangeable[7] and whether the benefits shown for one ACE inhibitor in a clinical trial can be extrapolated to the whole class of drugs, current clinical practice guidelines do not recommend specific ACE inhibitors but, rather, the whole class.[8–12] Moreover, no ACE inhibitor has proven to be superior for all indications.

Although few trials have been conducted on the ACE inhibitor ramipril, the Heart Outcomes Prevention Evaluation (HOPE) demonstrated this drug's effectiveness in the secondary prevention of cardiovascular disease.[13] HOPE was a Canadian-led, multicentre, randomized controlled trial involving 19 countries; the coordinating centre was in the province of Ontario. The purpose of the study was to assess the role of ramipril in patients who were at high risk for cardiovascular events but did not have left ventricular dysfunction or heart failure. The trial showed that treatment with ramipril reduced the rates of death, cardiovascular events, complications related to diabetes and the development of diabetes.[13,14]

HOPE was terminated early, in April 1999, because of the significant effect shown in interim analysis. The early termination was reported in Canadian newspapers in May 1999.[15,16] The final results of the trial were presented Aug. 31, 1999, at the European Society of Cardiology (ESC) Congress in Barcelona, received more newspaper publicity Sept. 1 in Canada,[17] were presented Nov. 10 at the American Heart Association Annual Meeting in Atlanta and on the *New England Journal of Medicine* Web site, and were published in print journals in January 2000.[13,14]

Previous studies have examined the impact of clinical trials on the prescribing of specific cardiovascular drugs.[18–20] We studied whether the prescribing of ACE inhibitors, and ramipril in particular, changed after the HOPE results were released.

Methods

Data sources

We used the Ontario Drug Benefit (ODB) database to identify all elderly residents of Ontario who were newly treated with an ACE inhibitor from Jan. 1, 1993, to Mar. 31, 2001. All Ontario residents aged 65 and over receive outpatient drug coverage from the ODB's minimally restrictive formulary. We studied the nine ACE inhibitors available in the formulary during the study period (benazepril, captopril, cilazapril, enalapril, fosinopril,

lisinopril, perindopril, quinapril and ramipril). Possible indications were identified with codes from the International Classification of Diseases, 9th revision (ICD-9-CM), in the Canadian Institute for Health Information (CIHI) hospital discharge database and the Ontario Health Insurance Plan (OHIP) physician claims database. The CIHI database contains information on the most responsible diagnosis and up to 15 secondary diagnoses for all hospitalizations in Ontario. The OHIP database records all fee-for-service billings for physician services in Ontario; it includes codes for all procedures and the most responsible diagnosis at each visit. Linkages across these databases are possible with the unique encrypted Ontario health card number, which is collected in all of these databases.

Identification of new ACE inhibitor users

We extracted all ODB claims from Jan. 1, 1992, to Mar. 31, 2001, for drugs dispensed under the classification of ACE inhibitor, excluding those for prescriptions filled in 1992 or for patients less than 66 years of age. This age cut-off was necessary because ODB does not take effect until age 65; people aged 65 could have been taking an ACE inhibitor previously, but their prescriptions would not be captured by the ODB until age 65. This process rendered a cohort of people that used an ACE inhibitor for the first time during the study period. We calculated the number of prescriptions filled in total and by individual drug to allow examination of trends for each ACE inhibitor.

Type of prescription filled for various indications

To examine whether the type of ACE inhibitor differed by indication and if the type changed after release of the HOPE results, we identified people who likely were started on an ACE inhibitor because of diabetes or congestive heart failure. We used the validated Ontario Diabetes Database, which combines ODB and OHIP claims,[21] and the CIHI hospital discharge database, searching the 4 previous years for admissions for congestive heart failure with ICD-9-CM codes 428.x (428.0 to 428.9).

Analysis

We examined prescribing patterns for January 1993 through March 2001 with the aim of identifying any immediate change following the first formal public release of the final HOPE results, Aug. 31, 1999. An immediate change was defined as a significant shift in prescribing pattern (i.e., a change in the monthly proportion of prescriptions attributable to each ACE inhibitor) from projected estimates within 5 months of the intervention. The data overall and for each type of ACE inhibitor were adjusted for estimated population changes using Ontario population data from the Registered Persons Database. We conducted time-series analysis,[22] using interventional autoregressive integrated moving average (ARIMA) models, to determine immediate effects within 5 lag periods following release of the HOPE results. Most time-series methods require the mean and variance of the data to remain the

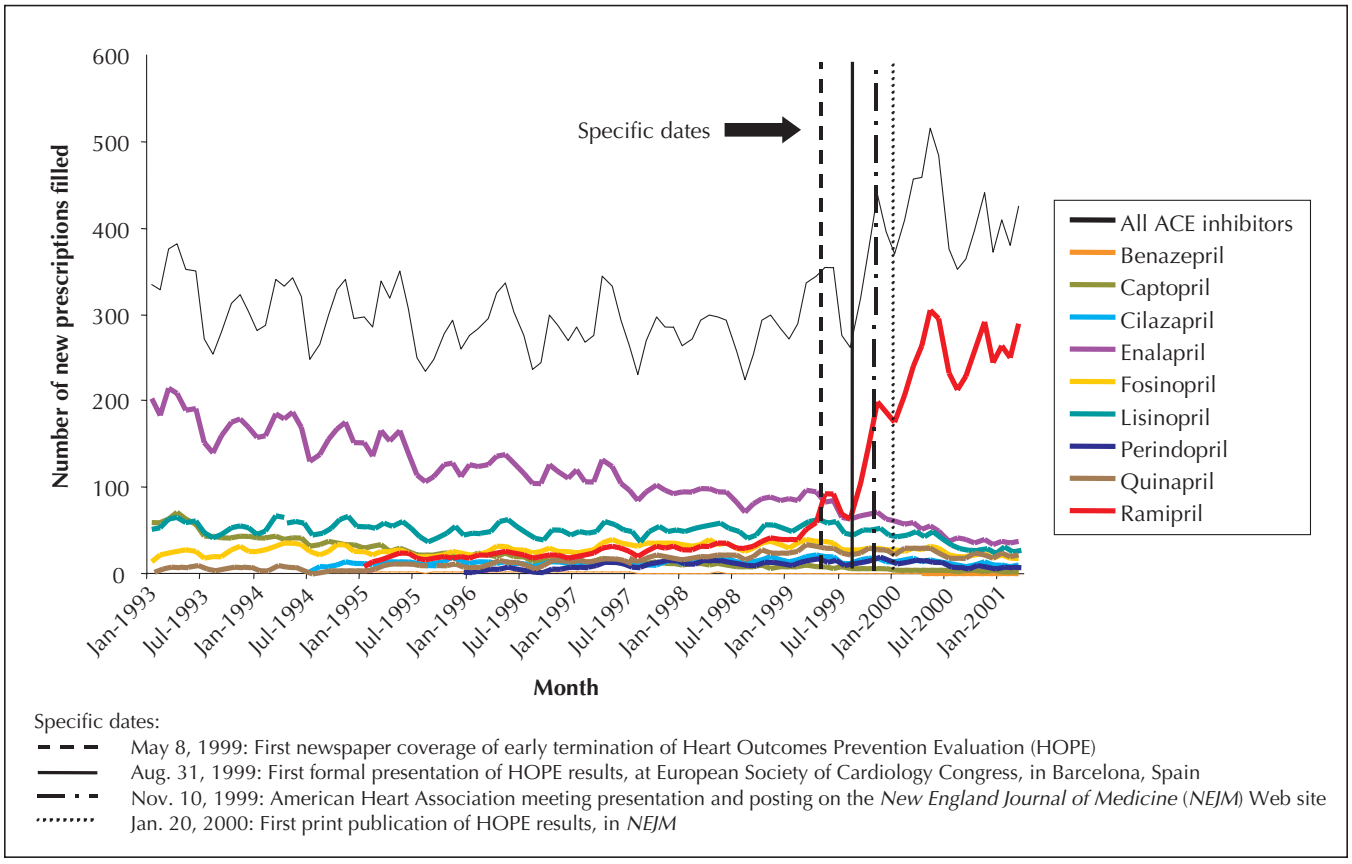

Fig. 1: Numbers of new prescriptions for angiotensin-converting-enzyme (ACE) inhibitors filled by elderly (aged 65 and over) Ontario residents.

same at all time points; if this requirement is met, the data are considered to be stationary. To assess this requirement in our analysis, we used the autocorrelation function and the augmented Dickey–Fuller test.[23] Autocorrelation, partial autocorrelation and inverse autocorrelation were assessed for model-parameter appropriateness and seasonality. The presence of "white noise" was assessed by examining the autocorrelations at various lags, using the Ljung–Box χ^2 statistic.[24] We also used interventional ARIMA modelling to examine changes in market share of the individual ACE inhibitors for specific indications. Two-sided p values are reported.

Results

Among the 1.29 million to 1.54 million elderly residents in Ontario, during the study period, the monthly number of new prescriptions for ACE inhibitors from 1993 to late 1999 was relatively constant and ranged from 224 to 382/100 000. However, with the release of the HOPE findings the rate increased significantly ($p < 0.01$), peaking at 515/100 000 in May 2000 (Fig. 1). This composite increase was primarily driven by the increase in ramipril prescriptions ($p < 0.01$).

From the introduction of ramipril in 1995 until the early termination of HOPE, in April 1999, the number of new monthly prescriptions filled for this drug reached a maximum of 58 per 100 000 elderly Ontario residents. In May 1999, the month of the first newspaper coverage of HOPE's early termination, the rate was 92/100 000. The rate dropped back to 63/100 000 in August 1999. After the first formal public release of the final HOPE results, on Aug. 31, at the ESC Congress in Barcelona, the rate increased significantly and reached a peak in May 2000 of 304/100 000 ($p < 0.01$), an increase of more than 400% over the maximum before HOPE's termination. None of the other ACE inhibitors showed any immediate significant changes in prescribing rate: benazepril, $p = 0.77$; captopril, $p = 0.93$; cilazapril, $p = 0.97$; enalapril, $p = 0.46$; fosinopril, $p = 0.35$; lisinopril, $p = 0.81$; perindopril, $p = 0.78$; and quinapril, $p = 0.84$.

Of the 448 976 elderly patients filling a new prescription for an ACE inhibitor during the study period, 23.7% (106 355) had diabetes and 12.3% (55 053) congestive heart failure. After formal release of the HOPE results the market share of ramipril among the various ACE inhibitors increased significantly ($p < 0.01$) among patients with diabetes (Fig. 2) or congestive heart failure (Fig. 3). In the diabetic population enalapril ($p = 0.03$), fosinopril ($p = 0.03$) and quinapril ($p = 0.04$) showed significant reductions in market share, and lisinopril ($p = 0.07$) and perindopril ($p = 0.07$) showed trends toward significant reductions. In the congestive heart failure population enalapril ($p = 0.01$), fosinopril ($p < 0.01$), lisinopril ($p = 0.02$) and quinapril ($p < 0.01$) showed significant reductions in market share.

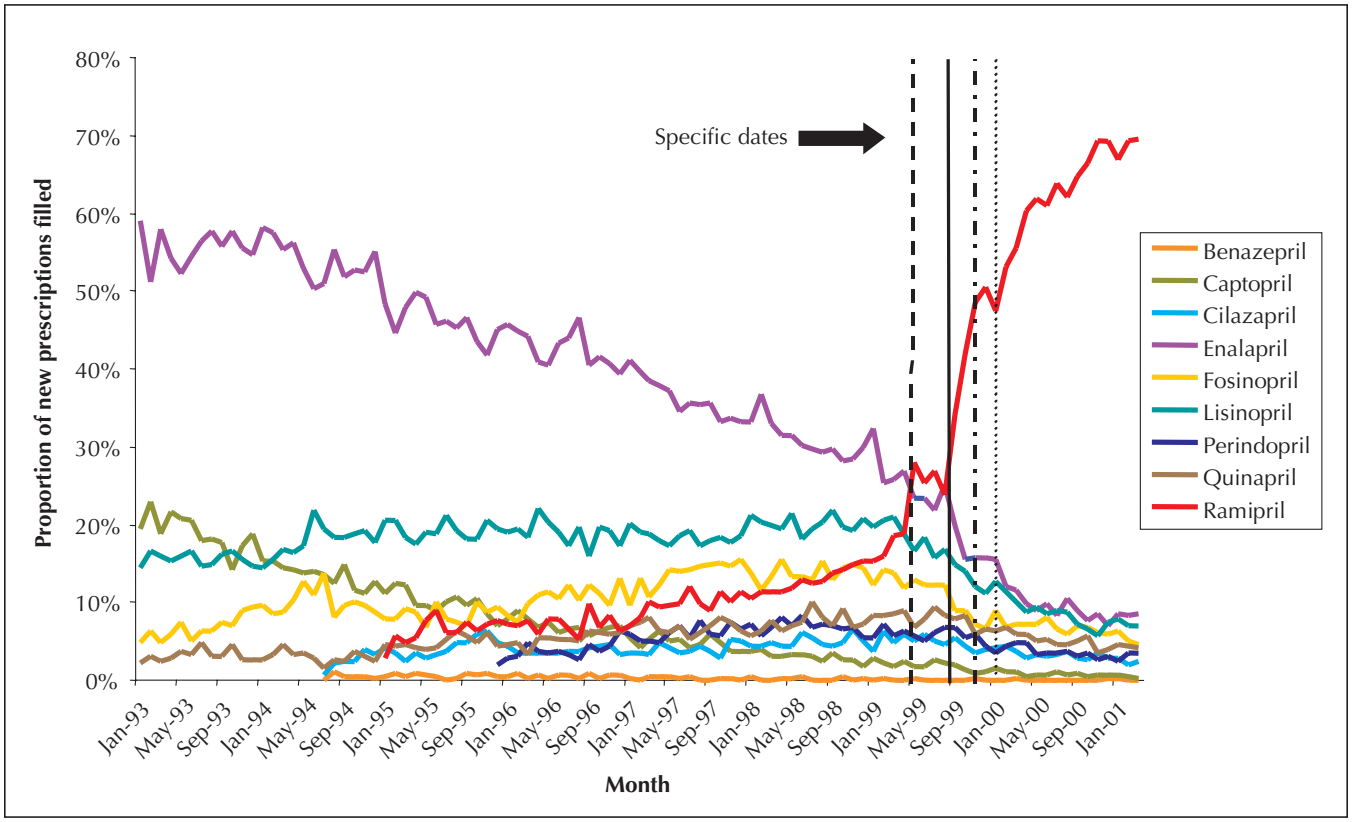

Fig. 2: Proportions of new prescriptions for specific ACE inhibitors among the elderly residents with diabetes mellitus. Specific dates as in Fig. 1.

Interpretation

Our results showed a clear and striking increase in the total number of elderly Ontario residents started on ACE inhibitor therapy, essentially due to an increase in ramipril prescribing, after release of the HOPE results. Compared with previous studies of the impact of clinical trials on specific cardiovascular drug therapy,[18–20] HOPE has shown the largest impact in terms of speed of uptake and magnitude of increase in prescribing within a year of trial completion.

Although it was not possible to determine the reasons for HOPE's impact, several factors are likely. First, the trial was coordinated by well-known researchers based in Ontario, had a large number of participants and had broad eligibility criteria compared with other cardiovascular trials. Second, the effect seen in the trial was both clinically and statistically significant, and ramipril had an effect across a number of clinically relevant outcomes. Third, ramipril is taken in a single daily dose, has a comparatively reasonable cost and is part of a class of relatively well-tolerated medications already familiar to most physicians. Last, HOPE was given considerable publicity in the lay and medical press, as well as promotion by the drug manufacturer.

Our study had several important limitations. Although administrative databases allowed us to study large populations and gave us an accurate picture of the drugs prescribed, all the criteria for inclusion in HOPE could not be measured with them. As well, although HOPE was an international multicentre trial, the primary investigators were from Ontario, and a large number of Ontario physicians and patients were involved in the trial. Thus, HOPE's impact could have been greater in Ontario than in places not involved in the trial. Last, pharmaceutical marketing changes physicians' prescribing behaviour.[25] However, the extent to which it contributed to the increase we observed could not be measured with the available data.

HOPE compared ramipril with placebo in patients at high risk for cardiovascular events. Although the MICRO-HOPE substudy showed ramipril to be efficacious in people with diabetes, it did not show this drug to be a superior ACE inhibitor in patients with congestive heart failure, as such patients were excluded. Our study showed that physicians have chosen ramipril over all other ACE inhibitors for elderly patients with diabetes or congestive heart failure. Although we cannot be certain about the long-term clinical effects of the changes we observed, HOPE's effect on prescribing is unprecedented.

This article has been peer reviewed.

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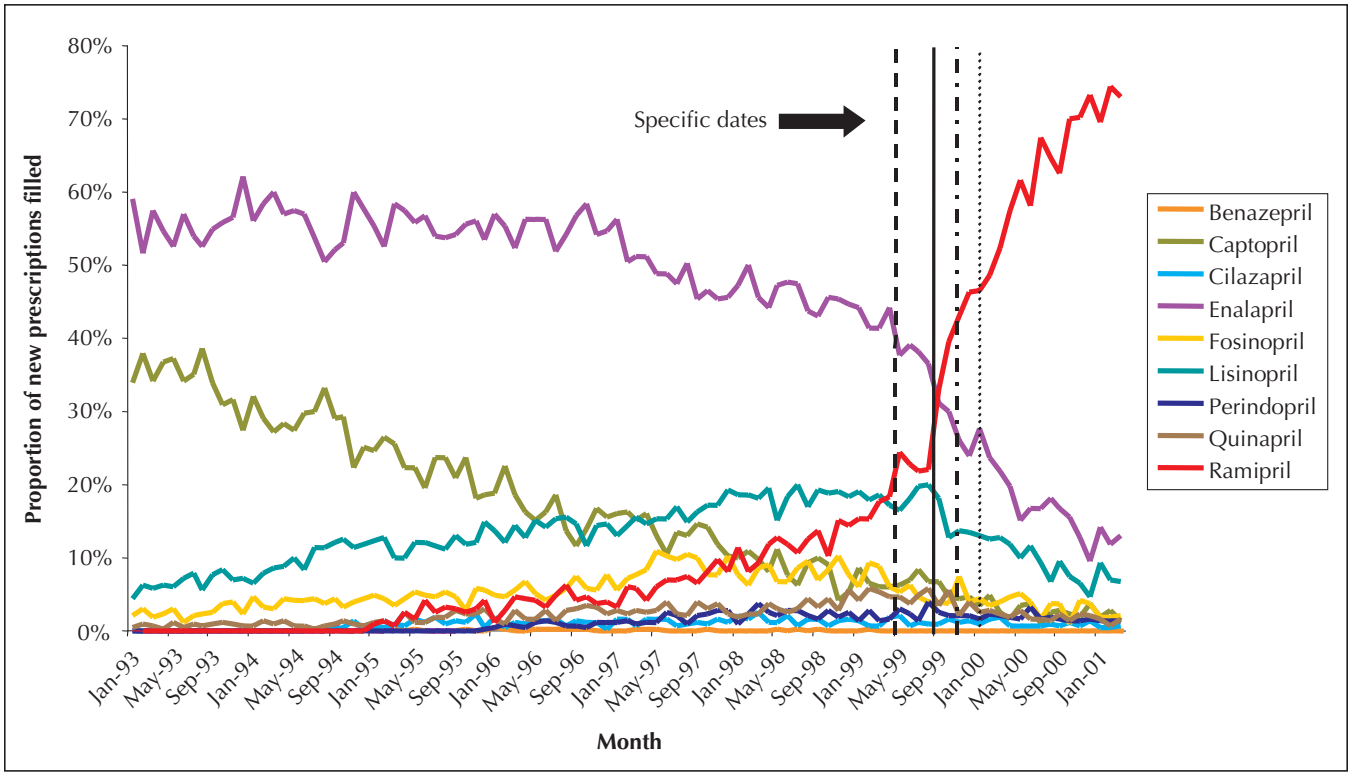

Fig. 3: Proportions of new prescriptions for specific ACE inhibitors among the elderly residents with congestive heart failure. Specific dates as in Fig. 1.

Competing interests: None declared.

Contributors: Dr. Karen Tu drafted the article and, along with Dr. Mamdani and Dr. Jack Tu, conceived and designed the study. Ms. Forde and Ms. Rothwell acquired the data. All authors analyzed and interpreted the data, revised the manuscript critically for important intellectual content and approved the final version.

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