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Competing interests: Dr. Brown has been a consultant for and has received speaker fees or educational grants from various pharmaceutical companies.

More than just hype

As researchers involved in the Heart Outcomes Prevention Evaluation (HOPE), we read with interest the article by Karen Tu and colleagues[1] and Louise Pilote's accompanying commentary.[2] As documented by Tu and colleagues for Ontario,[1] the HOPE results have had a striking impact on the prescription of ramipril, but Pilote's speculation[2] that HOPE's impact on practice is mostly in response to intense marketing ignores many relevant facts.

The HOPE study clearly demonstrated clinically important reductions in deaths, myocardial infarction, stroke, new heart failure, revascularization and nephropathy in a variety of subgroups.[3] In addition to these benefits, the evidence for the use of ramipril in a variety of conditions is extensive.[4-7] Furthermore, 4 independent analyses exploring the cost-effectiveness of ramipril[8-11] found clear clinical benefits with no overall increase in health care costs. Such a combination is rare.

Many cardiologists and internists across Canada became familiar with ramipril through their participation in the HOPE trial. It is therefore not unexpected that the study's positive results would have influenced the practices of these physicians and their colleagues, as was the case for previous trials of thrombolytic agents and acetylsalicylic acid in acute myocardial infarction.

Undoubtedly, the manufacturers of therapies for which benefits have been demonstrated will promote those findings. This certainly has an impact on their revenues, but it is only appropriate that, in the presence of clear evidence that a simple, safe and cost-effective therapy results in major improve-ments in patients' health, efforts be made to ensure that the results are widely known. Such dissemination of information will benefit both patients and society as a whole.

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Competing interests: The HOPE study was funded by CIHR, Aventis, HSFO, Astra, and vitamin E manufacturers. Dr. Yusuf has received speaker fees from several different companies who manufacture ACE and other drugs and has also received travel assistance, research grants, and an ongoing paid consultancy. Dr. Dagenais has received speaker fees for conferences related to the HOPE trial from Aventis and for a conference related to ACE-inhibitors from Merck-Frosst.

Clinical trial evidence has been accumulating to support the benefits of ramipril in a wide range of clinical applications. Yet Louise Pilote, in a recent commentary,[1] states that in most trials of angiotensin-converting enzyme (ACE) inhibitor therapy for patients with congestive heart failure, acute myocardial infarction or diabetes mellitus, ramipril was not the main ACE inhibitor studied.

Ramipril is the only ACE inhibitor shown to be beneficial in the prevention of adverse cardiovascular outcomes in diabetic patients with one risk factor for vascular disease. The Micro-HOPE study[2] showed that ramipril given for 4 to 5 years reduced cardiovascular mortality by 37% (relative risk 0.63, 95% confidence interval [CI] 0.49 to 0.79, $p = 0.0001$) among the 3657 diabetic patients enrolled in the HOPE study.[3]

Pilote goes on to report that of the 100 000 patients enrolled in trials of early administration of ACE inhibitors after acute myocardial infarction, none were assigned to receive ramipril. However, in the Acute Infarction Ramipril Efficacy (AIRE) study,[4] 2006 patients were randomly assigned to receive ramipril or placebo 3 to 10 days after acute myocardial infarction complicated by heart failure. After an average 15-month treatment period, there was an absolute risk reduction of 6% and a relative risk reduction of 27% for all-cause mortality (95% CI 11% to 40%, $p = 0.002$).

Pilote is correct in stating that only about 17% of patients in a clinical trial of ACE inhibitors were randomly assigned to receive ramipril.[5] However, there is substantial evidence supporting the use of ramipril for the prevention of heart failure from both the AIRE trial[4] and the HOPE study.[6] Furthermore, it is likely that the benefit of ACE inhibition in the management of heart failure is a class effect.

The large increase in the sales of ramipril after publication of the HOPE

study was driven by an excellent medical education campaign supported by a powerful landmark clinical trial. Is it not possible that application of the results of the HOPE trial in diabetic patients and in patients with vascular disease has saved many lives and that it has prevented numerous myocardial infarctions and strokes?

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Competing interests: Dr. Fichett has received speaker fees and travel assistance from Merck, BMS, Aventis and Servier.

A headline appearing in the highlights section of the March 4, 2003, issue of *CMAJ* was "The hype around HOPE," in reference to an article by Karen Tu and colleagues[1] and an accompanying commentary by Louise Pilote.[2] This expression was an appropriate play on words to describe changes in the prescribing of ramipril after publication of results from the large Canadian-led HOPE trial.

Reading these articles prompts questions about physicians' role in patient care. Will we continue to be led, like sheep, deeper and deeper into pharmaceutically driven disease management, or can we take charge by considering the real meaning of population health rooted in prevention?

Ramipril and other drugs are being investigated for their potential in preventing type 2 diabetes. But we already know how to prevent type 2 diabetes: lasting lifestyle change. Exercise and the maintenance of a stable, healthy weight prevent adult-onset diabetes. Let us not forget that 90% of type 2 diabetic patients are overweight, and many are obese — hence the recently coined term "diabesity."

Preventing type 2 diabetes through the use of drugs does not represent a success, nor is it honourable. Rather, it represents an abysmal failure and remains unbecoming of the medical profession, driving up health care costs while fuelling more disease and management research, not to mention the fact that all drugs, including those given for their beneficial effects, also have side effects.

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Competing interests: None declared.

Louise Pilote[1] implies that physicians who prescribed ramipril to more of their diabetic patients after the results of the HOPE study were publicized did so primarily because of marketing hype rather than solid research evidence. As a clinical epidemiologist and diabetes specialist, I am baffled by this position. The HOPE study[2,3] was by far the largest clinical trial evaluating an ACE inhibitor and enrolled a much broader clinical population than its predecessors. It included a prespecified subgroup of 3577 diabetic participants, possibly more than the total number of diabetic subjects enrolled in all previous ACE inhibitor trials. Diabetic (and nondiabetic) subjects assigned to receive ramipril had statistically and clinically significant risk reductions for major cardiovascular events. Strikingly, the results were homogeneous across all subgroups examined: male and female; with and without previous cardiovascular disease; younger than 65 years of age and 65 years and older; and with and without hypertension, microalbuminuria or dyslipidemia (or any combination of these comorbidities). Therefore, the HOPE study provided excellent evidence to support the use of ramipril in many diabetic patients who would not previously have been considered candidates for an ACE inhibitor. The HOPE study results are widely generalizable to older patients with diabetes because the great majority of such patients would have met the inclusion criteria for the study. The same cannot be said for any other ACE inhibitor trial.

Increased prescription of ramipril for diabetic patients based on the HOPE results represents not hype, but implementation of high-quality evidence from a large, adequately powered randomized trial.

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Competing interests: Dr. Sigal has received speaker fees and research support from Aventis, the manufacturer of ramipril.

[Louise Pilote responds:]

My commentary[1] elicited several letters supporting the results of the HOPE study. However, it was not