

protecting children and susceptible adults against much clearer threats to health, we as a nation have faltered. At present, only the rich can afford these effective vaccines. Underprivileged children, who are most at risk of a severe complication of infection and would benefit most from new vaccines, are least likely to receive them.<sup>5</sup>

The National Immunization Strategy<sup>2</sup> is a masterpiece of collaborative planning and a model for federal/provincial/territorial cooperation toward improved health. As an early step in current health care reforms, it offers an opportunity for the federal government to demonstrate its leadership in a role that will be deemed by most Canadians to be appropriate. Decision-makers might fear that it would result in a never-ending demand for funding of new and increasingly expensive vaccines. But this can be dealt with by agreeing on criteria — including economic considerations — for the assessment of new technology.

We must end the current provincial vaccination hodgepodge that results in treating some children (and adolescents and adults) as more precious than others. We urge you to act quickly to put into place a national coordinated system of planning, procurement, implementation, monitoring and evaluation. The status quo is a sure recipe for chaos.

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*Competing interests:* Drs. Naus and Scheifele participated in the planning of the 5th Canadian National Immunization Conference, held in Victoria, BC, in December 2002, and chaired planning workshops for the National Immunization Strategy.

*Contributors:* Dr. Naus was the principal author, and Dr. Scheifele contributed to the writing and revising of the manuscript. Both authors approved the final version.

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# Ramipril use in Canada: HOPE or HYPE?

Louise Pilote

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Angiotensin-converting-enzyme (ACE) inhibitors were developed for the treatment of hypertension. Subsequently they became indicated for several cardiovascular and renal conditions. ACE inhibitors play several roles: they alter the balance between the vasoconstrictive, salt-retentive and hypertrophic properties of angiotensin II, and they interfere with the vasodilatory and natriuretic effects of bradykinin and with the metabolism of other vasoactive substances.

ACE inhibitors have different chemical structures. As a result, they differ in potency, bioavailability, plasma half-life, route of elimination, distribution and affinity for tissue-bound ACE. Thus, their structural heterogeneity may reflect their functional heterogeneity.

In this issue (page 553), Tu and colleagues<sup>1</sup> report that after release of the results of the Heart Outcomes Prevention Evaluation (HOPE)<sup>2</sup> the monthly rate of new prescriptions for the ACE inhibitor ramipril filled by elderly (aged 65 and over) residents of Ontario rose more than 400%. Similar patterns were seen in most Canadian provinces

(Cynthia Jackevicius, Institute for Clinical Evaluative Sciences, Toronto, Ont.): personal communication, 2002). The monthly number of new prescriptions for all ACE inhibitors rose from 382/100 000 before the first formal release of the HOPE findings to 551/100 000 9 months later. The technique of time-series analysis took into account baseline temporal changes.

These striking results raise two important issues. First, is the extensive use of ramipril over other ACE inhibitors appropriate? Second, what factors led to the increase in ramipril prescription?

ACE inhibitors have been shown to be effective in treating essential hypertension,<sup>3</sup> renal disease<sup>4</sup> and congestive heart failure,<sup>5</sup> as well as in improving survival after acute myocardial infarction.<sup>6</sup> Although beneficial effects may occur with all drugs in this class, the extent to which they occur may vary.

In most trials of ACE inhibitor therapy for patients with congestive heart failure, acute myocardial infarction or diabetes mellitus, ramipril was not the main ACE inhibitor stud-

ied. For example, of 7105 patients with congestive heart failure, only 17.2% (1227) were randomly allocated to receive ramipril.<sup>5</sup> Of the 100 000 patients enrolled in trials of early administration of ACE inhibitors after acute myocardial infarction, none were randomly allocated to receive ramipril.<sup>6</sup>

HOPE enrolled patients at high risk of cardiovascular events — those with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus another cardiovascular risk factor. However, congestive heart failure was an exclusion criterion. Most patients with a history of acute myocardial infarction had suffered the infarction more than 1 year before. Only a third of the patients had diabetes.

Tu and colleagues found that after the first formal release of the HOPE results the use of ramipril increased among all elderly patients in Ontario, including those with congestive heart failure or diabetes. It therefore appears that physicians assume that ramipril is interchangeable with other ACE inhibitors. However, it remains to be seen how effective ramipril and other ACE inhibitors are for populations in which they have not been specifically studied.

The tendency for physicians to assume a class effect — that all drugs within a class exert the same effects, whether positive or negative, on their target population — is well illustrated by the striking increase in the prescription of ramipril, well above the prescription rates of other ACE inhibitors.

HOPE is one of the few large-scale trials conducted mostly in Canada and led by Canadian investigators. Intense marketing of the study occurred in hospitals, among attending staff and residents, and in the community. The marketing was so strong that the unusual rise in monthly number of ramipril prescriptions filled began before publication of the study results in the *New England Journal of Medicine* and *Lancet* in January 2000. As Tu and colleagues' Fig. 1 shows (page 554), the rise started in the fall of 1999, when the results were presented at a conference in Europe. Thus, most Canadian physicians knew about the study through enrolment of their patients or because of the widespread publicity.

Another factor that might explain the striking increase in

ramipril prescribing is the broad study population in HOPE, which may have allowed physicians to feel comfortable extrapolating the results to a large proportion of their patients. The study population had a variety of cardiovascular risks. Many physicians may have assumed that any person with cardiac risk factors would benefit from ramipril. However, the benefits for each subgroup remain unclear.

In conclusion, the rise in ramipril prescribing was due more to hype than to HOPE, as the striking increase was out of proportion to the evidence supporting use of this drug and was mostly in response to intense marketing.

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