blocker therapy for the composite outcome of cardiovascular death or nonfatal myocardial infarction, despite the occurrence of only 20 events (2 in the β-blocker group and 18 in the group receiving standard care). In contrast, the MaVS trial did not demonstrate a statistically significant effect with β-blocker therapy for the same composite outcome, even though there were 41 events (19 in the β-blocker group and 22 in the placebo group).

The MaVS trial also informs the issue of risk that Workman raises. In the MaVS trial more of the patients who received metoprolol had intraoperative bradycardia requiring treatment (53/247 v. 19/250, $p < 0.01$) and intraoperative hypotension requiring treatment (84/247 v. 26/250, $p < 0.01$).

Workman contends that because of duration of therapy and a multitude of concurrent medications, the effect sizes demonstrated in long-term β-blocker trials of patients with coronary artery disease and congestive heart failure do not inform the plausible magnitude of effect of β-blocker therapy in patients undergoing noncardiac surgery. Workman's contention is refuted, however, by the trials of β-blocker therapy in acute myocardial infarction, which have demonstrated relative risk reductions of 15% to 25% at 30-day follow-up,[4] and by current perioperative care, which often includes multiple medications and regional anesthesia. Finally, relative risk reductions beyond 35% are now extremely uncommon; hence our description of such results as "too good to be true."[5]

The results of the MaVS trial[2] reinforce the message that perioperative β-blockers have risks and as-yet-unproven benefits. Fortunately, a large, adequately powered trial that is now in progress, the PeriOperative Ischemic Evaluation (POISE) trial, should definitively establish the effect of perioperative β-blocker therapy in patients undergoing noncardiac surgery.

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Competing interests: P.J. Devereaux and Homer Yang are the principal investigators of the POISE Trial, Salim Yusuf is the chair of the POISE Steering Committee, Peter Choi is a member of the POISE Steering Committee, and Gordon Guyatt is a member of the POISE Steering Committee and the chair of the Adjudication Committee.

DOI:10.1503/cmaj.1041647

Patient–physician–regulator triad

We feel that the commentary by Gideon Koren and associates[1] regarding safety concerns related to isotretinoin has the potential to serve as a catalyst for safer use of this drug.

We concur that proper measures to prevent pregnancy in patients taking isotretinoin must be in place and that such measures must be user-friendly for both the health care provider and the patient. Implementation of safety measures should be consistent and universal, regardless of whether (or how many) generic forms of the drug have been authorized on the Canadian market. Currently, no approved generic isotretinoin products are available on the Canadian market, but approval of such generics would require a patient information program equivalent to the program now in effect for Accutane.

Health Canada attended the US Food and Drug Administration (FDA) advisory committee meeting on this subject in February 2004 and is aware of the FDA's proposal for tighter control of prescription of these drugs. Although the FDA had access to information suggesting a significant rate of pregnancy among women taking isotretinoin in the United States,[2,3] Health Canada's pharmacovigilance program, which includes but is not restricted to spontaneous reporting of adverse drug reactions and review of periodic safety update reports by the manufacturer, has shown no evidence of a comparable situation in Canada.

Part of Health Canada's mandate is to convey information that will minimize the risks and maximize the benefits of pharmaceutical products on the Canadian market. However, it will take more than regulatory due diligence to solve safety problems related to isotretinoin: endorsement of existing recommendations through physicians' daily practice remains an essential ingredient. Patients must also play an active role: once informed of a potential risk, their behaviour and compliance with the contraceptive methods become part of the equation, and closer follow-up must be planned if there is suspicion of noncompliance. The patient–physician–regulator triad is pivotal in optimizing the safe use of isotretinoin, as for any pharmaceutical product.

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Competing interests: None declared. The views expressed are those of the authors and do not necessarily reflect those of Health Canada.

DOI:10.1503/cmaj.1041643

[Two of the authors respond:]

As outlined in our commentary,[1] we agree that every effort should be made to prevent fetal exposure to isotretinoin, a highly teratogenic drug.

Maria Valois and associates state that, unlike the situation in the United States, Health Canada has no evidence of a significant rate of pregnancy among Canadian women taking isotretinoin. Unfortunately, this impression is incorrect. The presentations to the FDA in February 2004, attended by Health Canada, included a study by the Organization of Teratology Information Services,[2] which was funded by the US Centers for Disease Control and Prevention. More than half of the cases in that study came from Canada. The Canadian data were collected prospectively in 2002–2003 by The Motherisk Program (based in Toronto) and IMAGE (based in Montréal). On a proportional basis, Canada had substantially more cases than the United States.

This situation reflects the understandable ineffectiveness of reporting systems based on spontaneous reports. Moreover, in 2003 Health Canada stopped the development of MotherNet, a system that would have given the department such information continuously. The reason cited for the halt was lack of funding, although over $1 million had been spent on the project at that point.

Wouldn't it make sense for Health Canada to work with existing active surveillance programs in Toronto and Montréal and thus to receive the tremendous amount of data that are being collected on drugs in pregnancy in Canada? Presently, no arrangements exist for such collaboration.

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Competing interests: Neil Shear has received educational grants from Hoffmann-La Roche.

DOI:10.1503/cmaj.1041700

Outcomes of postmastectomy radiotherapy

In 1995 the American Society of Clinical Oncology adopted a statement on the choice of outcomes in assessing cancer treatments.[1] That statement made a clear distinction between patient outcomes (survival and quality of life) and cancer outcomes (tumour regression), the former being much more important. This view is also expressed in current books on cancer therapy.[2] A recently published guideline, though devoted to techniques of measuring tumour response, stated that this outcome is of value as an endpoint in early clinical trials, but in phase III trials and clinical application "it should not be the sole, or major, endpoint."[3] Yet the clinical practice guidelines published in *CMAJ* concerning the use of postmastectomy radiotherapy[4] appear to be founded entirely on evidence related to tumour responsiveness. Although local irradiation is effective in destroying local tumour tissue, none of the relevant clinical trials have shown that this leads to an improvement in overall survival. Normally, acceptance of a therapeutic modality requires demonstration of its efficacy, yet leading oncologists appear to take the opposite stance in regard to radiotherapy. Thus it is assumed, despite a lack of supporting evidence, that the majority of patients "require" irradiation but that subgroups who do not benefit will ultimately become recognizable.[5,6]

The authors of the guidelines are to be commended for including a "questions and answers" guide for women and their physicians (Appendix 1 of the article).[4] But one important question has been omitted: "How will radiation help me?" One must wonder how many of the patients anxiously waiting for radiation therapy are among those for whom therapy has been recommended despite a lack of evidence of benefit. If such patients were given balanced information and allowed to choose whether to undergo therapy, how many would decide against it?

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DOI:10.1503/cmaj.1041280