

of menopause-associated vasomotor symptoms: position statement of the North American Menopause Society. *Menopause* 2004;11(1):11-33.

Competing interests: None declared.

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We received no response from Dr. McIntyre and colleagues to our invitation to reply to these letters.

## Standards for pharmaceutical advertising in Canada

**R**ichelle Cooper and David Schriger<sup>1</sup> report their analysis of original research cited in pharmaceutical advertisements appearing in medical journals published in the United States. However, the standards for advertisements in US medical journals differ from those for Canadian ones. Almost all of the advertisements appearing in the latter are reviewed and precleared by the Pharmaceutical Advertising Advisory Board (PAAB). The standards of the PAAB “Code of Advertising Acceptance” are publicly available.<sup>2</sup>

Advertising reviewed and authorized by the PAAB must meet the following criteria:

- The advertisement must contain a list of references for medical claims. These references are analyzed by PAAB reviewers, who have received training in critical appraisal from expert academics teaching at leading Canadian medical schools.
- All references used to support claims must be provided to the PAAB during the review process, which provides assurance that they exist and are obtainable.
- All references used must be available to health care professionals on request.
- The advertisement must not contain data-on-file references unless such studies were part of a New Drug Submission reviewed by Health Canada.

Although not prohibited by the PAAB code, the fact that the majority of original research cited to substantiate claims is in some way affiliated with the product’s manufacturer is considered during the review process. The code re-

quires that “Clinical/therapeutic claims must be based on published, well-controlled and/or well-designed studies with clinical and statistical significance clearly indicated. Publication in peer-reviewed journals is usually a good criterion for establishing scientific rigor.”<sup>3</sup> This exceeds the standard for accredited continuing education events.

### Ray Chepesiuk

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### References

1. Cooper RJ, Schriger DL. The availability of references and the sponsorship of original research cited in pharmaceutical advertisements. *CMAJ* 2005;172(4):487-91.
2. Code of advertising acceptance. Pickering (ON): Pharmaceutical Advertising Advisory Board; 2005. Available: [www.paab.ca/index\\_en.html](http://www.paab.ca/index_en.html) (accessed 2005 Apr 26).

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### [The authors respond:]

**W**e thank Ray Chepesiuk for identifying important differences between Canada and the United States in the regulation of pharmaceutical advertisements and applaud the Canadian effort. Canadian regulations with regard to prerelease review of advertisements are unquestionably more stringent. We are concerned, however, that in neither country is the regulatory effort adequate to ensure that all of the relevant information is available to those making decisions about the effectiveness and cost-effectiveness of medications.<sup>1</sup> Although the pharmaceutical industry’s recent commitment<sup>2</sup> to make all clinically relevant trial data available on an industry-sponsored Web site ([www.clinicalstudyresults.org](http://www.clinicalstudyresults.org)) may help in this regard, at present much relevant material remains unpublished, and peer-reviewed publications often fail to tell the whole story.<sup>3</sup> Trial registry with electronic publication of research protocols before inception of each trial<sup>4,5</sup> and Web posting of complete data sets upon publication of the findings are 2 measures that could promote greater comprehensiveness and honesty in the reporting of trials.

Even if these measures are enacted, clinicians should remember that advertising exists to create a demand for a product and that claims made in advertisements may or may not be true. It is therefore imperative that all relevant information is on the table before clinicians and patients make decisions about the utility of medications. Despite increasing regulation, more remains to be done, and “caveat emptor” still applies.

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4. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al; International Committee of Medical Journal Editors. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *CMAJ* 2004;171(6):606-7.
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## Time-dependent analysis in CHF follow-up

**J**ustin Ezekowitz and colleagues<sup>1</sup> have concluded that patients with congestive heart failure who are followed by specialists and family physicians (FPs) experience better survival than patients who are followed by FPs alone; however, their analysis is not internally consistent.

In the Methods section they state, quite appropriately, that “[a] time-dependent analysis is essential when examining the effect of physician follow-up because patients’ outcomes can determine their

exposure.” Nevertheless, apart from a brief paragraph at the end of the Results section, all of their findings (in Tables 2 and 3 and in Fig. 1) are presented in terms of an inappropriate time-independent analysis that ignores any change in the provision of care during follow-up.

At the moment of discharge, all patients will have had no cardiovascular follow-up, and they will remain in that category until the first physician visit, at which time their status will change. Should that visit be to an FP, they will move into the FP-only category. Should they subsequently visit a specialist, they will move from the FP-only category to the combined (FP and specialist) category. From a methodologic point of view, these patients will leave behind the days at risk they experienced while in each of the preceding categories. A time-dependent Cox regression will assign them to the appropriate category in the risk set formed at the time of each death in the cohort. Neither the log-rank analysis of Fig. 1 nor the multiple logistic regression analysis of Table 3 make this correct comparison.

It is also not clear that the time-dependent Cox analysis mentioned in the last paragraph of the Results section has been done correctly. The authors state that the model was adjusted for “cumulative days spent in hospital within 1 year after discharge.” However, in a Cox analysis, the characteristics of subjects who died are compared with the characteristics of subjects still alive at the time of death of each case subject. The relevant variable would thus be time spent in hospital up to that time. Use of cumulative days within 1 year of discharge requires the use of future information. This is logically untenable.

I conclude that the authors’ results cannot be accepted at face value because their methods were inappropriate for their study design. I encourage them to compute the appropriate time-dependent models to answer this important question about management of congestive heart failure.

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## Reference

1. Ezekowitz JA, van Walraven C, McAlister FA, Armstrong PW, Kaul P. Impact of specialist follow-up in outpatients with congestive heart failure. *CMAJ* 2005;172(2):189-94.

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## [The authors respond:]

**M**urray Finkelstein is appropriately concerned about including postevent outcomes in a regression model. This would result in biased associations, namely, the inability to determine if the predictive factor resulted in the event or if the event resulted in the predictive factor. This has been called “survivor-treatment selection bias”<sup>1</sup> or, more generically, “time-dependent bias” and is relatively common even in highly cited medical journals. In a recent systematic review,<sup>2</sup> we found that 18.6% (95% confidence interval [CI] 15.8%–21.8%) of studies with a survival analysis contained a time-dependent factor and that 40.9% (95% CI 32.3%–50.0%) of these studies were susceptible to time-dependent bias.

However, we strongly disagree that our Cox model was performed incorrectly, since it was corrected for this bias. As stated in the Methods section, we adjusted for the appropriate time-dependent variables and did have a variable expressing time spent in hospital up to that time.<sup>3</sup> Our Results section summarizes the findings. The phrase “within 1 year after discharge” used there refers to the censoring time that we used for all analyses in the study. We did not use any “future information” and our methodology was robust.

In the Methods section, we note that we performed a sensitivity analysis using all outpatient visits rather than cardiovascular visits to define our groups; however, the results of this analysis were omitted by the journal because of space limitations. Using the same variables as in Table 3 but with all visits rather than cardiovascular visits, we found similar results: compared with those who had no outpatient visits, patients seen by a family physician (odds

ratio [OR] 0.80, 95% CI 0.64–0.96) or a specialist and family physician (OR 0.48, 95% CI 0.40–0.58) had lower mortality rates. Furthermore, similar results were obtained with the Cox model when all visits instead of cardiovascular visits were used: seeing a specialist was associated with lower mortality (hazard ratio 0.95, 95% CI 0.94–0.96).

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1. Glesby MJ, Hoover DR. Survivor treatment selection bias in observational studies: examples from the AIDS literature. *Ann Intern Med* 1996;124:999-1005.
2. Van Walraven C, Davis D, Forster AJ, Wells GA. Time-dependent bias was common in survival analyses published in leading clinical journals. *J Clin Epidemiol* 2004;57:672-80.
3. Ezekowitz JA, van Walraven C, McAlister FA, Armstrong PA, Kaul P. Impact of specialist follow-up in outpatients with congestive heart failure. *CMAJ* 2005;172(2):189-94.

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## Corrections

**T**he DOI attached to a recent News article<sup>1</sup> should have read 10.1503/cmaj.050548.

## Reference

1. Chéné C. Ads pressure Ontario to butt out in retail locations. *CMAJ* 2005;172(12):1544.

DOI:10.1503/cmaj.050835

**T**he DOI attached to a recent Query article<sup>1</sup> should have read 10.1503/cmaj.1040841.

## Reference

1. Query. *CMAJ* 2005;173(1):112.

DOI:10.1503/cmaj.050836