risk of cardiovascular disease." To make such a recommendation based on the adverse reactions presented in the newsletter is not scientifically rigorous. The data are not adjusted for exposure, and thus are unlikely to represent an accurate evaluation of cardiovascular risk.

The impetus behind this article appears to be a meta-analysis by Mukherjee and colleagues,[2] which is methodologically flawed[3–5] and does not form an appropriate basis for public health recommendations.

Certainly the increased rate of adverse cardiovascular events, as demonstrated in the VIGOR study for rofecoxib,[6] warrants further investigation. Clinical data available for celecoxib, however, demonstrate that patients on celecoxib are no more at risk of cardiovascular events than patients taking traditional NSAIDs such as ibuprofen, diclofenac or naproxen.[7] This observation holds true even at supratherapeutic doses, as demonstrated in the CLASS trial.[8,9]

Differences in molecular structure and metabolism may partly explain the distinct cardiovascular safety profiles of the 2 coxibs, and this hypothesis should be examined further.[10,11]

If immediate recommendations are required, perhaps Health Canada would be more justified in suggesting that caution be exercised in prescribing these agents, particularly rofecoxib, to patients at high risk of cardiovascular disease. The implementation of such a policy should be individualized at the discretion of the treating physician in light of each patient's risk factor profile, the presence (if any) of diabetes and cardiovascular history.

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Competing interests: Dr. Peterson has spoken for the last 2 years at continuing medical education events for Novartis, Merck, Pharmacia and Abbott.

References

1. Vu D, Murty M, McMorran M. Selective COX-2 inhibitors: suspected cardiovascular/cerebrovascular adverse reactions. *Can Adverse React Newsl* 2002;12(2):2-3.
2. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;286:954-9.
3. Haldey EJ, Pappagallo M. Cardiovascular events and COX-2 inhibitors [letter]. *JAMA* 2001;286 (22):2809-10.
4. Singh G. Cardiovascular events and COX-2 inhibitors [letter]. *JAMA* 2001;286(22):2810-1.
5. White WB, Whelton A. Cardiovascular events and COX-2 inhibitors [letter]. *JAMA* 2001;286 (22):2811-2.
6. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000;343 (21):1520-8, 2 p following 1528.
7. Celebrex product monograph.
8. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000;284(10):1247-55.
9. White WB, Faich G, Whelton A, Maurath C, Ridge NJ, Verburg KM, et al. Comparison of thromboembolic events in patients treated with celecoxib, a cyclooxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. *Am J Cardiol* 2002;89(4):425-30.
10. Zhao S, Reynolds M, Lefkowith JL, Whelton A, Arellano FM. Comparison of cardiovascular and renal adverse drug reactions (ADRs) between rofecoxib and celecoxib based on the WHO/UMC safety database. *Clin Ther* 2001;23(9):1478-91.
11. Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther* 2001;8:85-95.

In their report in the *Canadian Adverse Reaction Newsletter*,[1] Duc Vu and coauthors present their data in a table suggesting a comparison between the COX-2 agents without accounting for patient exposure or the fact that these drugs came onto the market at different times.

From this crude longitudinal data, the authors suggest that "caution should be exercised in prescribing these agents to patients at risk of cardiovascular disease." This recommendation is made even though the authors state that the "data cannot be used to determine the incidence of adverse reactions because neither patient exposure nor the amount of time the drug was on the market has been taken into consideration."

Although I recognize that Health Canada is attempting to take responsible measures for reporting adverse drug reactions, it is critical that inferences not be made when the data are provided without appropriate perspective. Reports such as these can do more harm than good by unnecessarily raising concern among physicians to the detriment of patient care. If Health Canada wants to improve adverse reaction reporting, it should look to evaluation procedures that combine information from postmarketing surveillance, epidemiologic research and clinical trials. The result will be a more comprehensive representation of data and one that appropriately reflects a therapy's safety profile and provides useful information to prescribing physicians.

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Competing interests: Dr. Raynauld received an honorarium and travel assistance to attend a meeting held by the Canadian Rheumatology Association. He has also received fees to speak about COX-2 inhibitors from Pharmacia, Pfizer, Merck and Genzyme.

Reference

1. Vu D, Murty M, McMorran M. Selective COX-2 inhibitors: suspected cardiovascular/cerebrovascular adverse reactions. *Can Adverse React Newsl* 2002;12(2):2-3.

[The editors of the *Canadian Adverse Reaction Newsletter* respond:]

The Marketed Health Products Directorate of Health Canada agrees that comprehensive risk–benefit evaluations should include information from postmarketing surveillance, epidemiologic research and clinical trials. However, in the absence of complete evidence, it is well recognized that spontaneous adverse reaction reports are nonetheless valuable in signalling a potential problem. Our newsletter is meant to provide observational results from the database. The safety of new drugs cannot be known with certainty until a drug has been marketed for many years.[1]

Although a relation between the cardiovascular findings and the use of rofecoxib and celecoxib has not been established at this time, Health Canada, as a precaution, deems it necessary to inform health professionals and advises patients with a medical history of hypertension, fluid retention or heart fail-