Not fast enough?

In their report on accelerated publication in medical journals,[1] William Ghali and colleagues were apparently not asked to update their citation counts beyond December 1999, although their study was published more than 2 years later. I attempted to replicate their citation analysis for the 12 articles from the *New England Journal of Medicine*, using citation data updated to April 2002. Interestingly, I found that the *Science Citation Index* grossly underestimated the citation count for one paper[2] because of a known problem with indexing of articles with group authorship.[3]

With corrected and updated data, the average citation rate was nearly twice as high for the 6 prereleased articles as for the 6 controls (50 v. 30 citations per year). Importantly, the control articles as well as the prereleased articles had citation rates well above the average for articles published in the journal in the same year (1.6 and 2.7 times higher, respectively). Citation rates for prereleased articles and their matched controls were not independent but were highly correlated (Spearman correlation coefficient = 0.88; $p = 0.02$).

The latter observation illustrates a major flaw underlying Ghali and colleagues' study as a whole: overmatching, which is biased against finding differences between accelerated and control articles. Although the stated objective of the study was to compare accelerated articles to a journal's "usual" output, the control articles were purposely chosen to be as similar as possible in subject and design to the case articles. Use of random controls would have been a fairer and more informative way to meet the study's objective.

For articles published in leading medical journals, the subject of a study appears to have a greater influence on its impact than the particular study itself. Despite this, accelerated articles were found to have higher importance scores in every dimension than nonaccelerated articles on the same topic. Although prerelease of articles is a relatively new phenomenon, journal editors appear to have been generally successful in expediting articles that are more important and will be more widely cited.

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[The authors respond:]

We thank Matthew Stanbrook for his interest in our article.[1] He offers some useful new information on citation counts that reinforces one aspect of our findings.

Readers may recall that citation counts were an ancillary outcome of our study. The primary outcome was clinical importance as rated by specialists with research training. By that measure, we demonstrated significant differences favouring expedited publication. As the closing paragraph of our article stated, "Our results lead us to conclude that policies for expedited publication are, on average, targeting important articles and may be contributing to the visibility of research findings" — a conclusion that is entirely in keeping with the global conclusion that Stanbrook makes in his letter. The new citation averages that he provides reinforce that assessment.

Stanbrook is perhaps defending the editorial status quo in claiming that overmatching is a "major flaw" in our study. In fact, it is precisely because the subject of study has a major impact on perceived clinical importance and citation counts that we opted for matched controls rather than randomly chosen controls. Had we randomly selected our control articles, readers could have rightly argued that we were making apple-to-orange comparisons that biased our results in favour of expedited publication.

In sum, articles selected for accelerated publication have, on average, higher ratings of clinical importance, and, as Stanbrook usefully elucidates, higher average citation counts. However, some control articles were rated as more important than case articles, a finding that should not be ignored or dismissed by journal editors. There may be better ways of capturing very important articles, and we thus reiterate that journal editors should continue to evaluate and refine their selection policies for accelerated publication.

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COX-2 inhibitors in the treatment of cardiovascular disease

In a recent *Canadian Adverse Reaction Newsletter*[1] issued by Health Canada, the authors recommend that "caution should be exercised in prescribing [selective COX-2 inhibitors] to patients at

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.

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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.

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[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-