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Increase in Nonfatal Digestive Perforations and Haemorrhages following Introduction of Selective NSAIDs: a Public Health Concern

We read with interest the paper by Barnard et al.[1] titled 'Increase in nonfatal digestive perforations and haemorrhages following introduction of selective NSAIDs: a public health concern'. We agree with the authors' conclusions that the prevalence of the use of selective NSAIDs increased, and the use of non-selective NSAIDs decreased, during the study period. We also agree, as stated by the authors, that "… a causal link between selective NSAID use and nonfatal digestive perforations and haemorrhages cannot be established from the data reported …". The study methods and results do not support such an inference. Nor do they support the notion that cyclo-oxygenase (COX)-2 selective inhibitors are relatively more toxic to the gastrointestinal (GI) system than non-selective NSAIDs in persons at equal GI risk, as some might mistakenly conclude from the results. It is for this reason that we would like to point out major limitations to this study that were not adequately addressed and that severely limit the interpretation of the data.

First, given the results of well designed GI endpoint trials that demonstrated the GI safety advantage of COX-2 selective inhibitors relative to non-selective NSAIDs,[2-4] it is not surprising that many patients previously using non-selective NSAIDs, especially those with GI risk factors, switched to COX-2 inhibitors. It is also reasonable to assume that some of the increase in prevalence of COX-2 use was due to new use by patients who were not using NSAIDS at all because of prior intolerance or GI complication while taking non-selective NSAIDs in the past. Because of this differential uptake of COX-2 inhibitors, those prescribed these drugs have been shown to have a greater GI risk profile than those prescribed non-selective NSAIDs.[5,6] However, the study by Barnard et al.[1] did not adjust for such differences among COX-2 and non-selective users in their accounting of GI outcomes in these groups.

Second, the GI outcomes were assessed from physician claims. Some of these claims may have been to 'rule out' diagnoses. In a recent study, Rahme et al.[7] reviewed hospital charts of 30 patients obtained from the Montreal General Hospital-McGill University Health Centre on the basis of an *International Classification of Diseases* (9th Edition) code (principal or secondary) for upper GI perforations and haemorrhages appearing on the discharge summary. They found that only 13 (43%) of these patients had such diagnoses on admission. If this misclassification were operative in the Barnard study, the bias would go against the COX-2 selective inhibitors because, as reported elsewhere and by the authors, more patients prescribed them had prior GI risk. Information about the validity of the claims used to ascertain GI endpoints in the study are needed to judge the study's validity.

Lastly, the authors compared the percentages of patients with GI events during different annual time periods without taking into account differences in person-time of exposure between the groups. This approach is highly likely to be biased. Since the prevalence of COX-2 selective inhibitor use and of long-term NSAID use (overall) increased over time, it is reasonable to assume that the person-time at risk for the COX-2 selective group was greater than that for the non-selective NSAID group. In such a situation, the bias would be against the COX-2 inhibitors.

COX-2 selective inhibitors are not free of GI risk and they should be used judiciously in patients at risk of GI events. However, well designed endoscopic surveillance studies,[8,9] GI outcomes tri-

als[2-4] as well as a combined analysis of clinical trials of rofecoxib that examined low and high GI risk subgroups[10] have shown they are safer than non-selective NSAIDs in persons at equal GI risk.

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