Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: informahealthcare.com/journals/ieds20

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Response to: BROPHY JM: Celecoxib and cardiovascular risks. *Expert Opin. Drug Saf.* (2005) 4(6):1005-1015.

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To cite this article: Bernard Bannwarth (2006) COX-2 selective drugs and cardiovascular risks: same data but discrepant conclusions?, Expert Opinion on Drug Safety, 5:1, 1-2, DOI: 10.1517/14740338.5.1.1

To link to this article: https://doi.org/10.1517/14740338.5.1.1

Published online: 22 Dec 2005.

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Expert Opin. Drug Saf. (2006) 5(1):1-2

I enjoyed reading the article by Dr Brophy [1] who should be commended for a comprehensive and well-informed review of celecoxib and cardiovascular risks. Dr Brophy concluded that 'the complete evidence from both the randomised trials and from observational studies suggests that any increased cardiovascular risk with celecoxib is most likely small, less than rofecoxib and comparable to most traditional NSAIDs' [1]. In fact, the similarity in adverse events profiles between compounds belonging to the same drug class does not preclude the possibility that one agent of this class may exhibit an increased specific risk. In other words, there may be a gradient of cardiovascular risk across coxibs [2,3]. Conversely, a US Food and Drug Administration (FDA) memo, posted on the FDA website on April 15, 2005 [101] indicated that 'the available data do not permit a rank ordering of (the three approved COX-2-selective NSAIDs; celecoxib, rofecoxib and valdecoxib) with regard to cardiovascular risk'. As a medical practitioner, one may be puzzled that discrepant conclusions could be drawn from theoretically similar data.

One reason for this discrepancy is that the FDA advisory panel focused on the combined end point of death from cardiovascular causes, myocardial infarction, and stroke whilst Dr Brophy considered congestive heart failure and hypertension too. In that respect, there is some evidence that rofecoxib has a greater effect on blood pressure than celecoxib [4]. This may have significant cardiovascular risk implications in the long-term [2]. Furthermore, Dr Brophy while acknowledging the limitations of observational studies, stressed that rofecoxib, unlike celecoxib, was reported to be associated with an increased cardiovascular hazard in most retrospective cohort and case-control studies [1]. On the other hand, the FDA advisory panel considered that observational data could not definitively address the issue of the relative risk for serious cardiovascular adverse events among available NSAIDs [101]. Thus, a second explanation for the discrepancy between Dr Brophy's conclusions and those of the FDA advisory panel is that the latter was sceptical about the reliability of observational studies because of their inherent biases and residual confounding.

Conflict of interest

The author has attended Merck sponsored symposia as an invited speaker and was involved in clinical studies sponsored by Merck.

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Author's response

Dr Bannwarth raises the very interesting point regarding the often radically different conclusions that may occasionally be enounced despite the same evidence base. Specifically, he notes that the FDA advisory panel was unable to stratify risks between the different COX-2 inhibitors, whereas I concluded that celecoxib is most likely safer than rofecoxib. This is largely explained by the inclusion of the totality of the evidence in my decision-making process, including well-designed observational studies. Although it is true that observational studies may exhibit bias and residual confounding, the same issues may arise in poor quality randomised clinical trials. The COX-2 observational studies of adverse outcomes have the advantage of 100-fold larger, unselected populations which is in sharp contrasted to the small and highly selected populations studied in the clinical trials.

There are a number of methodological safeguards that can be followed to improve the quality of observational studies including a scientifically rigorous study design, such as a nested-case control [5]. The validity of the COX-2 observational studies appears confirmed as they generally detected the increased rofecoxib cardiovascular risk as seen in the randomised studies. As the rofecoxib observational findings suggest a lack of study bias, it seems reasonable to assume internal consistency and to also accept the demonstrated lack of excess risk for celecoxib as likely having equal veracity.

What is clearly important is that our decision-making processes be systematic, rigorous and utterly transparent so that our readership can then make their own informed decisions.

James M Brophy, McGill University Health Centre, Canada

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Website

101. http://www.fda.gov/cder/drug/infopage/cox2 Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular riks.

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