

Observational studies and the withdrawal of rofecoxib[†]

Félix M. Arellano^{1,2*}

¹Risk Management Resources, Califon, NJ, USA

²Visiting Fellow, St. Vincent's Clinical School, Faculty of Medicine, University of New South Wales, Sydney, Australia

Watson and Santanello's reply¹ to my editorial² reveals some of the problems that resulted in the withdrawal of rofecoxib. One is the misinterpretation of statistical significance tests as synonymous of causality. Watson and Santanello state that the study by Solomon *et al.*³ 'showed no significantly increased risk with rofecoxib when compared with no NSAID use or with use of various non-selective NSAID' . . . but 'a small increased risk with rofecoxib compared with celecoxib (OR = 1.24; 95%CI 1.05–1.46)'. Indeed, the results for the comparison against non-use and NSAID use were OR = 1.14 (95%CI 1.0–1.31) and 1.17 (95%CI 0.99–1.38), respectively. Any inference on causality drawn from the three results must be identical as the results are essentially indistinguishable.^{4,5} Misinterpretation of statistical significance such as this may have led to the statement that the results from clinical and epidemiologic (observational) studies before APPROVe⁶ were 'inconsistent'.¹ However, before the results from APPROVe became available, the data from clinical trials showed little or no increased risk of MI with 25 mg/day use, and an increased risk with 50 mg/day.⁷ Already in 2001⁸ a meta-analysis of clinical trials published in 2001 did not show an increased risk of thromboembolic events with doses of 12.5–25 mg/day compared with NSAID, but with 50 mg/day there was an indication of an elevated risk of thromboem-

bolic events RR = 2.08 (95%CI 0.57–7.51) which was disregarded because of its 'lack of statistical significance'. Figure 1 shows the results of VIGOR,⁷ APPROVe⁶ and the available epidemiologic studies that compared the risk of developing acute myocardial infarction (MI) in rofecoxib users compared to non-use.^{3,9–13} The studies by Ray⁹, Mamdami,¹³ Solomon³ and Graham¹⁰ and VIGOR⁷ were published or made public before APPROVe.⁶ Thus, the epidemiologic studies available at the time and those published after APPROVe showed consistent results and confirmed the dose response pattern.

A second problem is that FDA and Watson and Santanello¹ place an over reliance on clinical trial data and refer to epidemiologic data as not 'robust' enough for 'regulatory decision-making'. Regarding the lack of 'robustness' of epidemiologic data, drug labels are routinely updated with data from spontaneous reports which are considered even less 'robust'. In 2002, rofecoxib's label¹⁴ was updated to include information on the increased risk of MI based on the results of the VIGOR⁸ trial, but not on any data from epidemiologic studies. If the label of a drug is aimed at guiding physicians in the use of a drug in clinical practice, it is difficult to understand why data from epidemiologic studies reflecting the actual use of rofecoxib in clinical practice, were ignored. Likewise, rofecoxib's withdrawal was based on data from APPROVe, where the increased risk of thromboembolic events became apparent after 18 months and was found to be 'significant' after 36 months of continuous use.⁶ If an average patient treated with rofecoxib at 25 mg/day needs to be on the drug continuously for at least 18 months to be at risk, most patients treated in clinical practice are not on the drug for that long. Indeed, continuous rofecoxib use for ≥ 1 year is exceptional ($\leq 2\%$) in clinical practice,¹⁵

*Correspondence to: Félix M. Arellano, Risk Management Resources, 1200 Route 22 East, Suite 2000, Bridgewater, NJ 08807, USA.

E-mail: arellanofm@msn.com

[†]The author was the Chief Safety Officer of Pharmacia, prior to its acquisition by Pfizer. Risk Management Resources is a consultant to several pharmaceutical companies, including Merck.

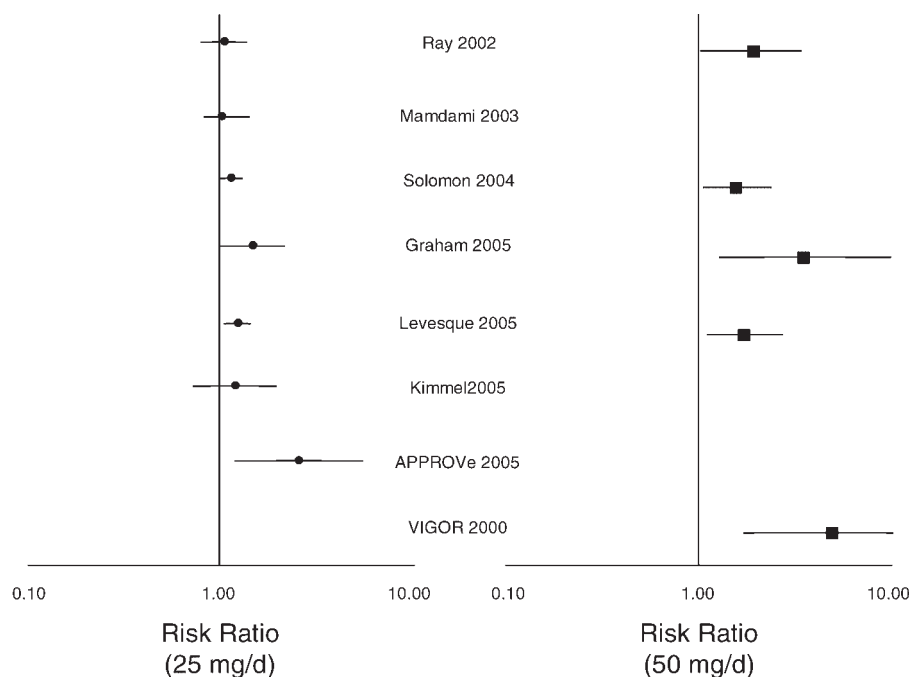


Figure 1. Risk of myocardial infarction in patients treated with rofecoxib compared to non-users in epidemiologic studies, VIGOR and APPROVe. Comparators were: non use for Ray,⁹ Mamdami,¹³ Solomon,³ Levesque¹¹ and Kimmel¹²; “remote” use for Graham¹⁰; placebo for APPROVe⁶ and naproxen for VIGOR⁷

explaining why previous clinical trials and most epidemiologic studies failed to demonstrate an increased risk associated with rofecoxib used at 25 mg/day. Thus, rofecoxib was withdrawn based on the results of a study that had limited relevance for the vast majority who use the drug.

All research studies have limitations as well as strengths. Whenever the results of nonexperimental epidemiology are interpreted, inevitably some critic will remind us of its ‘inherent bias’,¹⁶ as Watson and Santanello have done here.¹ But experimental epidemiology—clinical trials—has limitations also, including the underestimate of the effect of received treatment with ‘intent-to-treat’ analyses, and a study population that may differ markedly from the patient population who use the drug. The withdrawal of rofecoxib should serve as a reminder, among other things, of the lack of applicability to clinical practice ‘inherent’ to clinical trials.

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