

Cardiovascular safety of rofecoxib (Vioxx): lessons learned and unanswered questions

We need processes in place to follow up suspicions about serious adverse events

Rofecoxib and a second cyclooxygenase-2 (COX-2) inhibitor, celecoxib, were approved by the Therapeutic Goods Administration in 1999 after large phase III randomised trials showed they were as effective as “traditional” non-steroidal anti-inflammatory drugs in reducing pain and inflammation and less likely to cause gastric ulceration.^{1,2} Since then, COX-2 inhibitors have become one of the 10 most widely used prescription medicines in Australia, at a cost to the federal government of more than \$200 million annually.³ However, uncertainty has surrounded the cardiovascular safety of rofecoxib (Vioxx; Merck Sharp & Dohme), and COX-2 inhibitors as a class, ever since an increased risk of cardiovascular events was reported among patients randomly allocated to the rofecoxib group in the VIGOR trial.¹

On 7 September this year, Merck Sharp & Dohme faxed a “Dear Doctor” letter to Australian doctors to reassure them of the cardiovascular safety of rofecoxib. Yet, 3 weeks later, Merck Sharp & Dohme suddenly announced an immediate worldwide withdrawal of rofecoxib; this action is the largest prescription drug withdrawal in history. In response, the United States Food and Drug Administration (FDA) immediately issued a public health advisory on rofecoxib, while Australia’s Therapeutic Goods Administration issued a customer-level recall for an estimated 250 000–300 000 Australians taking the drug.⁴

The first concern about the cardiovascular safety of rofecoxib emerged with the VIGOR study, reported in 2000. It involved a fivefold increase in myocardial infarction and a twofold increase in myocardial infarction, stroke or cardiovascular death among 8076 rheumatoid arthritis patients treated for a median of 9 months with rofecoxib compared with naproxen¹ (see Box). Further questions about the cardiovascular safety of rofecoxib were raised in 2001 by an overview of the clinical trial data.⁶ These data prompted the FDA to initiate a label change in 2002, highlighting the potential cardiovascular risks of rofecoxib. Despite more recent observational studies also suggesting an increased early (within the first 30 days of treatment) and late (beyond 30 days) risk of acute myocardial infarction or sudden cardiac death with rofecoxib,^{7,8} conclusive evidence of increased cardiovascular risk from adequately powered randomised trials was lacking.⁹

The decision by Merck to withdraw rofecoxib worldwide was prompted by an unexpected source. APPROVe (Adenomatous Polyp Prevention On Vioxx) was a multicentre, placebo-controlled trial of 2600 patients designed to examine the effects of treatment with rofecoxib on the recurrence of neoplastic polyps of the large bowel in patients with a history of colorectal adenoma.⁴ An interim analysis of this trial demonstrated an almost twofold increase in cardiovascular events in patients treated with rofecoxib (25 mg daily) compared with placebo (see

Box). When these data are extrapolated to the Australian population, the increased risk of 16 events per 1000 patients treated for up to 3 years equates to a potential excess of several thousand cardiovascular events caused by rofecoxib. This may represent an underestimate of the number of events caused by rofecoxib, because patients with inflammatory arthritis are likely to be at higher baseline risk of cardiovascular events than the “low risk” population included in APPROVe.⁴

The dramatic withdrawal of rofecoxib raises important questions for clinicians, pharmaceutical companies and regulatory authorities.

What is the basis for the increased cardiovascular risk?

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) suppress prostaglandin synthesis by inhibiting both constitutively expressed COX-1 (primarily responsible for “housekeeping” functions such as gastric protection and haemostasis) and the inducible COX-2 (which is upregulated in inflammatory conditions). The coxibs (COX-2-selective NSAIDs) do not inhibit production of platelet thromboxane (a potent platelet agonist and vasoconstrictor), but selectively suppress endothelial prostacyclin (an intrinsic vasodilator and platelet inhibitor). It has been hypothesised that selective inhibition of prostacyclin production by coxibs without concomitant platelet inhibition leads to thrombosis in at-risk individuals.^{10,11} However, alternative hypotheses suggest that blockade of COX-2 in atheromatous plaques may reduce vascular inflammation and the progression of vascular disease, and perhaps even prevent events.^{9,12}

Is the thrombotic risk a class effect?

The celecoxib studies have not demonstrated an increased risk of thrombosis,^{2,7,8} but there are no long-term safety studies. Several second-generation coxibs have recently been approved for use in the United States (Lumiracoxib, Valdecoxib) and Europe (Etoricoxib, a derivative of rofecoxib). While randomised trials involving these drugs have not shown a significant increase in thrombosis risk,^{13,14} they have not excluded it. Consequently, their potential risk for causing cardiovascular events has also been questioned.^{8,11} Given the clear demonstration of increased cardiovascular risk with rofecoxib, it is now incumbent on drug manufacturers and regulatory authorities to demonstrate cardiovascular safety for all existing and new coxibs.

What are the alternative therapeutic options?

Paracetamol-based analgesia is widely recommended as first-line therapy to reduce chronic pain. However, when used alone, paracetamol appears to be less effective than NSAIDs,¹⁵ and there are no studies of the safety of the long-term intake of paracetamol.

...what are the lessons learned
by pharmaceutical and regulatory
bodies...

Cardiovascular outcomes in major phase III randomised trials of the cyclooxygenase-2 (COX-2)-selective inhibitors approved for use in Australia

COX-2-selective agent	Trial	No. of patients	Comparator	Cardiovascular outcome	Absolute risk (absolute risk increase; 95% CI)	No. needed to harm*
Rofecoxib	VIGOR 2000 ^{1†}	8076	Naproxen	MI, stroke, death	1.1% v 0.5% (0.6%; 0.3%–1.0%)	167
	ADVANTAGE 2003 ^{5†}	5557	Naproxen	MI, stroke, death	0.4% v 0.3% (0.1%; –0.2 to 0.4%)	—
	APPROVe 2004 ⁴	2600	Placebo	MI, stroke	3.5% v 1.9% (1.6%; 0.3–2.8%)	62.5
Celecoxib	CLASS 2000 ²	8059	Ibuprofen or diclofenac	MI, stroke, angina	0.9% v 1.0% (–0.1%; –0.5 to 0.4%)	—

MI = myocardial infarction.

*Number of patients who need to be treated in order to cause one adverse cardiovascular outcome. †Patients taking aspirin were not eligible for inclusion.

NSAIDs are indicated for patients with inflammatory arthritis. For those at increased risk of gastrointestinal complications, the options include celecoxib or a traditional NSAID combined with a proton-pump inhibitor. Neither of these strategies has been tested in patients with cardiovascular disease.

What can be done to prevent a recurrence of similar problems with future (new) drugs?

Regulatory authorities in Australia and overseas were prepared to accept that an increased rate of cardiovascular events in the VIGOR study was the result of a protective effect of naproxen rather than a toxic effect of rofecoxib. In retrospect, it would have been better if systems had been put in place to further investigate the increased risk of cardiovascular events with rofecoxib when these were first evident. Robust and consistent processes to suspect and actively examine such outcomes need to be established and implemented, particularly when life-threatening effects are possible with symptomatic treatments for non-life-threatening conditions.

At the end of the day, the real question is what are the lessons learned by pharmaceutical and regulatory bodies from this sorry tale? Pfizer, the manufacturer of Celebrex, has recently announced that it will sponsor a major clinical study to reassess the cardiovascular safety of its product.¹⁶ However, the outcome is some time off.

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Competing interests: Dr Langton has given advice to and/or talks for a variety of pharmaceutical companies, including Pfizer and Merck Sharp & Dohme.



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