REVIEW

COX-2 inhibitors and the heart: are all coxibs the same?

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The selective COX-2 inhibitors (coxibs) were originally developed to minimise the adverse effects of conventional non-steroidal anti-inflammatory drugs (NSAIDs) while maintaining the same analgesic and anti-inflammatory properties. Many large studies confirmed the improved gastric side effect profile of coxibs compared with non-selective NSAIDs; however, reports of increased cardiovascular morbidity and mortality followed, and the manufacturer Merck was forced to withdraw rofecoxib (Vioxx) from the market. Other coxibs have also either perished or had restrictions placed on their use. However, there seem to be significant differences between coxibs regarding their cardiovascular profiles, and the evidence for a class effect is dubious. In this paper, the current body of knowledge regarding the cardiovascular toxicities of coxibs is reviewed. The take home message for prescribing NSAIDs and those coxibs still on the market seems to be one of caution rather than contraindication, except in patients with significant cardiovascular risk factors.

There is a conflicting body of data in the literature regarding the association between the use of selective cyclo-oxygenase-2 inhibitors (the so called coxibs) and adverse cardiac events.[1] Coxibs were first introduced as alternative analgesics to conventional non-steroidal anti-inflammatory drugs (NSAIDs). The approval of rofecoxib (Vioxx) and celecoxib (Celebrex) by the Food and Drug Administration (FDA) in the USA came in 1999 with their subsequent market release. As the coxibs are specific for the COX-2 isoform of the cyclo-oxygenase enzyme it was believed that they would cause fewer side effects than non-selective NSAIDs. Numerous large scale studies confirmed that coxibs did cause fewer gastric side effects than non-selective NSAIDs,[2–6] and the National Institute for Health and Clinical Excellence (NICE) in the UK recommended that all patients at risk of gastric side effects, including all patients over the age of 65, who needed a NSAID should receive a coxib.[7] Before its FDA approval, 5435 patients had taken rofecoxib, generally as part of small, short term trials; however, even at that time the medical officer of the FDA observed ''that in six-week studies, thromboembolic events are more frequent in patients receiving rofecoxib (12 (0.67%) of 1780) than placebo (1 (0.24%) of 412)''.[8] This finding did not stop the subsequent granting of approval from the FDA.

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The Vioxx gastrointestinal outcomes research (VIGOR) trial[2] was a large clinical trial that randomised patients with rheumatoid arthritis to rofecoxib 50 mg/day or naproxen 1000 mg/day. The trial found a twofold reduction in gastrointestinal events in the rofecoxib arm, but also showed a fivefold increase in the incidence of acute myocardial infarction in the rofecoxib arm when compared with the naproxen arm.[2] This resulted in a longer projected life expectancy for the average rheumatoid arthritis patient taking naproxen compared with the patient taking rofecoxib.[9] It is unclear at present whether the gastrointestinal side effect profile with coxibs is superior to a conventional NSAID combined with a proton pump inhibitor,[10] and indeed even whether the analgesic effects of coxibs are superior to NSAIDs,[11] further questioning the rationale for their use. Because there was no placebo arm in the VIGOR trial these findings could suggest either an adverse cardiac effect of rofecoxib or a previously unrecognised protective cardiac effect of naproxen.

It has been proposed that coxibs may adversely influence the prostacyclin (antithrombotic): thromboxane (prothrombotic) ratio in the vascular wall. Coxibs may inhibit the production of prostacyclin (antithrombotic) and leave thromboxane (prothrombotic) generation unaffected (as there are no COX-2 receptors in platelets), thus promoting platelet aggregation and atherosclerosis.[12–14] Furthermore, inhibition of prostacyclin in the kidney could lead to sodium and water retention, causing hypertension.[15] These biological actions might increase the risk of cardiovascular events, including myocardial infarction and stroke.[14] The mechanism postulated for naproxen's possible cardioprotective effect is its inhibition of thromboxane with consequent platelet aggregation,[12] and some authors have suggested combination therapy with non-selective NSAIDs to combat this.[16]

A recent nested case-control study by Graham *et al*[17] examined a cohort of patients treated with an NSAID between 1 January 1999 and 31 December 2001, using data from the Kaiser Permanente. The Kaiser Permanente is a national integrated managed care organisation providing comprehensive health care to more than 6 million Californians, and thus a huge database that identified 2 302 029 person years of follow up. Of these, there were 8143 cases of serious coronary heart disease, each of which were risk-set matched with four controls on age, sex, and health plan region. The multivariate odds ratio was 1.59 (95% confidence interval 1.10 to 2.32)

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; COX-2, cyclo-oxygenase-2

for all doses of rofecoxib, 1.47 (0.99 to 2.17) for 25 mg or less daily, and 3.58 (1.27 to 10.11) for doses greater than 25 mg daily, all compared with celecoxib. Celecoxib was not associated with any increased risk of cardiac events compared with remote (greater than two months ago) NSAID use (odds ratio 0.84, 0.67 to 1.04), while naproxen was found to confer a slightly increased risk (odds ratio 1.14, 1.00 to 1.30). Of further interest in this study is that the mean time to occurrence of a cardiac event was less than four months, suggesting that the cardiovascular risk of rofecoxib begins soon after the drug is started. The authors concluded that between 88 000 and 140 000 excess cases of serious coronary heart disease might have resulted from the use of rofecoxib rather than other NSAIDs or coxibs in the USA alone since its market launch in 1999.

Juni *et al*[18] performed a standard and cumulative random effects meta-analysis of 18 randomised clinical trials identified from bibliographies and files of the FDA. They showed that by the end of 2001, those patients taking rofecoxib had a relative risk of myocardial infarction of 2.24 (1.24 to 4.02) compared with the control arm. Of particular note is the finding that this relative risk did not change with the control drug used, be it placebo, naproxen, or a non-naproxen NSAID. A UK study[19] examining coxib and NSAID use in primary care found a significantly increased risk of myocardial infarction associated with current use of rofecoxib (odds ratio 1.32, 1.09 to 1.61) compared with no use in the previous three years; with current use of diclofenac (1.55, 1.39 to 1.72); and with current use of ibuprofen (1.24, 1.11 to 1.39). Increased risks were also associated with the other coxibs and non-selective NSAIDS compared with no use of NSAIDs or coxibs. However, this study was observational in design, and therefore may be subject to confounding, making its results less certain.[19 20]

The recently published adenomatous polyp prevention on Vioxx (APPROVe) trial[21] examined the effects of rofecoxib on the incidence of benign sporadic colonic adenomas (known precursors of colon cancer). The manufacturers of rofecoxib, Merck, were forced to withdraw Vioxx from the market after the premature halting of the study by the external safety review board because of the finding that the group assigned to rofecoxib had a fourfold increased risk of serious thromboembolic events (mainly acute myocardial infarction and cerebrovascular accident) compared with the placebo group.[3] Vioxx had achieved the most impressive global sales growth for any drug in 2001 with worldwide sales topping $US 2.5 billion in 2004.[22] It is estimated that 80 million people worldwide had taken Vioxx before its withdrawal.[22] There is currently much litigation against Merck as a result of its aggressive marketing programme despite earlier safety warnings about the drug.[3]

As well as confirming an adverse risk cardiovascular profile for rofecoxib, the above studies do suggest that celecoxib is safer. Hudson *et al*[23] undertook a retrospective cohort study that included more than 2000 patients aged over 65 who were prescribed celecoxib, rofecoxib, or a non-selective NSAID at their index admission for congestive cardiac failure. They found that the combined risk of death and recurrent congestive cardiac failure was higher in patients prescribed rofecoxib or NSAIDs than in those prescribed celecoxib (hazard ratios 1.27 and 1.26 respectively). The celecoxib long term arthritis safety study (CLASS)[24] was published in 2000 and compared celecoxib with either ibuprofen or diclofenac in patients with osteoarthritis or rheumatoid arthritis, and found no difference in the rates of myocardial infarction. However, CLASS also found no difference in adverse gastrointestinal events between the groups and, therefore, this study provides clinical evidence that celecoxib is less COX-2 selective than rofecoxib.[24 25] A 10-fold reduction on COX-2 specificity for celecoxib compared with rofecoxib has also been found using whole cell assays.[26]

By the time of the withdrawal of rofecoxib, many second generation coxibs with improved COX-2 selectivity had been released on the market. These include valdecoxib, parecoxib, etoricoxib, and lumiracoxib.[27] The therapeutic arthritis research and gastrointestinal event trial (TARGET)[28] found a hazard ratio of 1.77 (95% CI 0.82 to 3.84) for myocardial infarctions in patients assigned lumiracoxib compared with naproxen. A recent randomised trial that compared valdecoxib (and its intravenous prodrug, parecoxib) with placebo for pain relief in patients undergoing coronary artery bypass surgery found an increased incidence of myocardial infarction and cerebrovascular accident at 30 days after just 10 days in the valdecoxib arm.[29–31]

Further ongoing trials looking at the newer coxibs as well as the older agents are awaited, but unfortunately they are mostly being performed in patients with rheumatoid arthritis as in CLASS and TARGET. It is known that rheumatoid arthritis itself is a risk factor for cardiac disease, probably because of a chronic heightening of circulating cytokine concentrations as well as C reactive protein and other pro-atherogenic inflammatory markers, with activation of leucocytes in both processes.[32 33] This is also thought to be the case for other chronic inflammatory conditions that typically require long term analgesia.[34] Furthermore, this patient population tends to be elderly, and the risk of adverse drug events may not be comparable to a younger population.[7 35] Hence, these studies will not answer the question of the risk: benefit ratio of short term use of these drugs in patients at little or no risk for adverse cardiac events. This is a crucial issue in discovering if the coxibs are safe in a chemopreventive role.

In contrast with the above studies suggesting that safety concerns regarding coxibs do not extend to celecoxib, the adenoma prevention with celecoxib (APC) trial[36] was suspended by the US National Cancer Institute when it was found that patients taking 400 mg and 800 mg daily celecoxib had a 2.5-fold and 3.4-fold increase respectively in their risk of experiencing a major cardiovascular event compared with patients on placebo. A further randomised study of celecoxib in patients with Alzheimer's disease also showed unfavourable cardiovascular outcomes in the drug arm.[37]

All of the above studies that have been published are summarised in table 1, listed in the order they have been discussed in the text.

CONCLUSIONS

The Medicines Healthcare products Regulatory Agency (MHRA), the European Medicines Agency (EMEA), and the Committee on Safety of Medicines (CSM) have all formulated guidelines on the prescribing of coxibs. The CSM have sent their guidelines to all UK doctors[38 39] (similar guidelines are issued by the EMEA):

- A contraindication is introduced for all COX-2 inhibitors in patients with ischaemic heart disease or stroke
- A warning is introduced for prescribers to exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease, such as hypertension, hyperlipidaemia, diabetes, and smoking, as well as for patients with peripheral arterial disease

The MHRA have added that ''patients treated with any COX-2 inhibitor who have established ischaemic heart disease or cerebrovascular disease should be switched to

Table 1 The major studies of coxibs and cardiovascular morbidity

Study	N=	Indication	Study design	Adverse cardiovascular events
VIGOR (2000)[2]	8076	Rheumatoid arthritis	Double blinded RCT (rofecoxib compared with naproxen)	RR of MI in naproxen group was 0.2; overall mortality and death from cardiovascular causes similar
Graham *et al* (2005)[17]	All patients aged 18–84 treated with an NSAID over a three year period from a 6 million population database (2302029 person years)	Various—no strict criteria	Nested case-control study of cardiac events	Compared with celecoxib RR for rofecoxib was 1.59. For naproxen compared with remote NSAID use the adjusted OR was 1.14
Juni *et al* (2004)[18]	21432	All bibliographic databases and files of the FDA that compared rofecoxib with other NSAIDs or placebo, and trials of cardiovascular risk and naproxen	Meta-analysis of 18 RCTs and 11 observational studies	RR of MI for rofecoxib compared with placebo, naproxen, or other NSAIDs was 2.24
Hippisley-Cox and Coupland (2005)[19]	9218 cases and 86349 matched controls	Primary care patients taking coxibs and NSAIDs over a five year period	Nested case-control study using QRESEARCH database (of 367 UK GP surgeries)	Adjusted OR compared to no use of NSAID in past three years for rofecoxib was 1.32, for diclofenac was 1.55, and for ibuprofen was 1.24. Increased risks were also found for other coxibs and NSAIDs albeit less dramatic.
Bresalier *et al* (2005) (APPROVe)[21]	1287 cases and1299 controls	History of colorectal adenomas	Double blinded RCT (rofecoxib compared with placebo)	RR of confirmed thrombotic event (for example, MI, CVA) for rofecoxib was 1.92 compared with placebo
Hudson *et al* (2005)[23]	2256	Patients aged ⩾66 prescribed celecoxib, rofecoxib, or a NSAID after index admission for CCF over a two year period	Population based retrospective cohort study of hospital discharge summary and prescription drug databases	Hazard ratio for death and recurrent CCF combined was 1.26 for patients prescribed NSAIDs or rofecoxib compared with celecoxib
Silverstein *et al* (2000) (CLASS)[24]	8059	Patients aged ⩾18 with osteoarthritis or rheumatoid arthritis	Double blinded RCT (celecoxib compared with ibuprofen or diclofenac)	No difference in cardiovascular events between celecoxib and NSAIDs
Farkouh *et al* (2004) (TARGET)[28]	18325	Patients aged ⩾50 with osteoarthritis	Double blinded RCT (lumiracoxib compared with naproxen or ibuprofen)	Harzard ratio for MI for lumiracoxib compared with naproxen was 1.77 (non-significant) and for lumiracoxib compared with ibuprofen was 0.75 (non-significant)
Nussmeier *et al* (2005)[31]	1671	Patients with postoperative pain after CABG	Double blinded RCT (parecoxib plus valdecoxib compared with placebo plus valdecoxib compared with placebo alone)	RR for cardiovascular events (for example, MI, CVA, PE, cardiac arrest) for parecoxib plus valdecoxib compared with placebo was 3.7)
Soloman *et al* (2005) (APC)[36]	2035	History of colorectal adenomas	Double blinded RCT over three years (celecoxib low dose compared with celecoxib high dose compared with placebo)	Hazard ratios for death from cardiovascular causes (for example, MI, CVA, CCF) compared with placebo for low dose (200 mg twice daily) celecoxib was 2.3 and for high dose (400 mg twice daily) celecoxib was 3.4

alternative (non-COX-2 selective) treatments as soon as is convenient''.[40] The FDA has also issued similar guidelines.[41] Alternative drugs include conventional NSAIDs, paracetamol, and opioids.

There are published studies on cardiovascular adverse events with rofecoxib, celecoxib, and the newer agents parecoxib and valdecoxib. The evidence cited in this review shows that their cardiovascular safety profiles are not the same, and that celecoxib is probably the safest. This is most probably because of its lower specificity for the COX-2 enzyme. However, published evidence cited in this review also suggests that cardiovascular concerns extend to non-COX-2-specific NSAIDs such as diclofenac and ibuprofen, and it remains to be elucidated whether celecoxib is safer than these conventional NSAIDs. It is also unclear whether the risk:benefit profile of celecoxib is superior to conventional NSAIDs plus gastric protection with a proton pump inhibitor, and further studies are needed to investigate this. At present it seems that celecoxib is the coxib of choice but that it does have adverse cardiac effects if used for prolonged periods, especially at high doses.

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