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. 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 cyclooxygenase 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. The Vioxx gastrointestinal outcomes research (VIGOR) trial 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. This resulted in a longer projected life expectancy for the average rheumatoid arthritis patient taking naproxen compared with the patient taking rofecoxib. 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, and indeed even whether the analgesic effects of coxibs are superior to NSAIDs, 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 athero-sclerosis. Furthermore, inhibition of prostacyclin in the kidney could lead to sodium and water retention, causing hypertension. These biological actions might increase the risk of cardiovascular events, including myocardial infarction and stroke. The mechanism postulated for naproxen’s possible cardioprotective effect is its inhibition of thromboxane with consequent platelet aggregation, and some authors have suggested combination therapy with non-selective NSAIDs to combat this.

A recent nested case-control study by Graham et al 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 al35 performed a standard and cumulative random
effects meta-analysis of 18 randomised clinical trials identi-
fied 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 study36 examining coxib and NSAID use in
primary care found a significantly increased risk of myocar-
dial 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.37 38

The recently published adenomatous polyposis prevention
on Vioxx (APPROVe) trial39 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
arm.37

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)39
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 under-
going 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.35 36

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
proatherogenic inflammatory markers, with activation of leuco-
cytes in both processes.34 35 This is also thought to be the case
for other chronic inflammatory conditions that typically
require long term analgesia.34 Furthermore, this patient
cohort population tends to be elderly, and the risk of adverse
drug events may not be comparable to a younger population.36
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 chemopreven-
tive role.

In contrast with the above studies suggesting that safety
concerns regarding coxibs do not extend to celecoxib, the
adenoma prevention with celecoxib (APC) trial35 was
suspected 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 formu-
lated guidelines on the prescribing of coxibs. The CSM have
sent their guidelines to all UK doctors30 31 (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, hyperlipi-
daemia, 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
alternative (non-COX-2 selective) treatments as soon as is convenient.” The FDA has also issued similar guidelines. 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 thecoxib of choice but that it does have adverse cardiac effects if used for prolonged periods, especially at high doses.

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Table 1  The major studies of coxibs and cardiovascular morbidity

<table>
<thead>
<tr>
<th>Study</th>
<th>N=</th>
<th>Indication</th>
<th>Study design</th>
<th>Adverse cardiovascular events</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIGOR (2000)</td>
<td>8076</td>
<td>Rheumatoid arthritis</td>
<td>Double blinded RCT (rofecoxib compared with naproxen)</td>
<td>RR of MI in naproxen group was 0.2; overall mortality and death from cardiovascular causes similar. Composed with celecoxib RR for rofecoxib was 1.59. For naproxen compared with remote NSAID use the adjusted OR was 1.14.</td>
</tr>
<tr>
<td>Graham et al (2005)</td>
<td>All patients aged 18–84 treated with an NSAID over a three year period from a 6 million population database (2302029 person years)</td>
<td>Various—no strict criteria</td>
<td>Nested case-control study of cardiac events</td>
<td>RR of MI for rofecoxib compared with placebo, naproxen, or other NSAIDs was 2.24.</td>
</tr>
<tr>
<td>Juni et al (2004)</td>
<td>21432</td>
<td>All bibliographic databases and files of the FDA that compared rofecoxib with other NSAIDs or placebo, and trials of cardiovascular risk and naproxen</td>
<td>Meta-analysis of 18 RCTs and 11 observational studies</td>
<td>RR of MI for rofecoxib compared with placebo, naproxen, or other NSAIDs was 2.24.</td>
</tr>
<tr>
<td>Hippisley-Cox and Coupland (2005)</td>
<td>9218 cases and 86349 matched controls</td>
<td>Primary care patients taking coxibs and NSAIDs over a five year period</td>
<td>Nested case-control study using QRESEARCH database (of 367 UK GP surgeries)</td>
<td>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.</td>
</tr>
<tr>
<td>Bresalier et al (2005)</td>
<td>1287 cases and 1299 controls</td>
<td>History of colorectal adenomas</td>
<td>Double blinded RCT (rofecoxib compared with placebo)</td>
<td>RR of confirmed thrombotic event (for example, MI, CVA) for rofecoxib was 1.92 compared with placebo. Hazard ratio for death and recurrent CCF combined was 1.26 for patients prescribed NSAIDs or rofecoxib compared with celecoxib.</td>
</tr>
<tr>
<td>Hudson et al (2005)</td>
<td>2256</td>
<td>Patients aged ≥66 prescribed celecoxib, rofecoxib, or a NSAID after index admission for CCF over a two year period</td>
<td>Population based retrospective cohort study of hospital discharge summary and prescription drug databases</td>
<td>Double blinded RCT (celecoxib compared with ibuprofen or diclofenac)</td>
</tr>
<tr>
<td>Silverstein et al (2000)</td>
<td>8059</td>
<td>Patients aged ≥18 with osteoarthritis or rheumatoid arthritis</td>
<td>Double blinded RCT (lumiracoxib compared with naproxen or ibuprofen)</td>
<td>Hazard ratio for MI for lumiracoxib compared with naproxen was 1.77 (non-significant) and for lumiracoxib compared with ibuprofen was 0.75 (non-significant).</td>
</tr>
<tr>
<td>Farkouh et al (2004)</td>
<td>18325</td>
<td>Patients aged ≥50 with osteoarthritis</td>
<td>Double blinded RCT (parecoxib compared with placebo plus valdecoxib compared with placebo alone)</td>
<td>Hazard ratios for death from cardiovascular causes (for example, MI, CVA, CCF) compared with placebo low dose (200 mg twice daily) celecoxib was 2.3 and for high dose (400 mg twice daily) celecoxib was 3.4.</td>
</tr>
<tr>
<td>Nussmeier et al (2005)</td>
<td>1671</td>
<td>Patients with postoperative pain after CABG</td>
<td>Double blinded RCT (parecoxib plus valdecoxib compared with placebo plus valdecoxib compared with placebo alone)</td>
<td>RR for cardiovascular events (for example, MI, CVA, PE, cardiac arrest) for parecoxib plus valdecoxib compared with placebo was 3.7</td>
</tr>
<tr>
<td>Solomon et al (2005)</td>
<td>2035</td>
<td>History of colorectal adenomas</td>
<td>Double blinded RCT over three years (celecoxib low dose compared with celecoxib high dose compared with placebo)</td>
<td>No difference in cardiovascular events between celecoxib and NSAIDs.</td>
</tr>
</tbody>
</table>

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