Are COX-2 inhibitors preferable to non-selective non-steroidal anti-inflammatory drugs in patients with risk of cardiovascular events taking low-dose aspirin?

Vibeke Strand

Cyclooxygenase-2 selective inhibitors and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) are associated with increased risk of acute cardiovascular events. Only aspirin offers primary and secondary cardiovascular prophylaxis, but trials have not answered directly whether low-dose aspirin is cardioprotective with COX-2 inhibitors. A large inception cohort study showed that concomitant use of aspirin reduced risk of cardiovascular events when given with rofecoxib, celecoxib, sulindac, meloxicam, and indometacin but not when given with ibuprofen. In large trials assessing gastrointestinal safety, there were fewer gastrointestinal events in patients using both COX-2 inhibitors and aspirin than in those using non-selective NSAIDs and aspirin; significantly fewer uncomplicated upper gastrointestinal events took place in the MEDAL trial. Analysis of VIGOR and two capsule endoscopy studies showed significantly less distal gastrointestinal blood loss with COX-2 inhibitors than with non-selective NSAIDs. Endoscopy trials showed that low-dose aspirin does not diminish the gastrointestinal benefits of COX-2 inhibitors over non-selective NSAIDs. In an elderly epidemiological cohort receiving aspirin, both celecoxib and rofecoxib reduced risk of admission for gastrointestinal events. Comparison of the cardiovascular and gastrointestinal risks is difficult: likelihood and severity of cardiovascular events differ between individuals, agents, and exposure. Mortality associated with gastrointestinal events is less frequent than with cardiovascular events, but asymptomatic ulcers can result in severe complications. Data support the conclusion that COX-2 inhibitors are preferable to non-selective NSAIDs in patients with chronic pain and cardiovascular risk needing low-dose aspirin, but relative risks and benefits should be assessed individually for each patient.

Introduction

Patients with chronic pain and known risk factors for acute thromboembolic cardiovascular events pose a dilemma for physicians; chronic pain must be alleviated otherwise patients will not remain active, further increasing their cardiovascular risk. Although cyclooxygenase-2 (COX-2) selective inhibitors were developed to reduce the adverse gastrointestinal effects of non-selective non-steroidal anti-inflammatory drugs (NSAIDs), both classes of drug are associated with increased risk of acute cardiovascular events. Only aspirin offers primary and secondary prophylaxis against cardiovascular events, but it cannot be taken in doses high enough for anti-inflammatory effects because of tolerability problems. Important questions remain about relief of chronic pain in patients with cardiovascular risk. First, does low-dose aspirin offer protection against cardiovascular events associated with non-selective NSAIDs or COX-2 inhibitors? Second, are gastrointestinal benefits associated with COX-2 inhibitors lost if low-dose aspirin is used as prophylaxis for cardiovascular events? Third are COX-2 inhibitors rather than non-selective NSAIDs preferable on the basis of gastrointestinal benefits versus cardiovascular risk if low-dose aspirin is taken as prophylaxis? Data from randomised controlled trials and large epidemiological studies can inform these decisions. This review summarises these data to encourage work to establish the magnitude of cardiovascular risk associated with non-selective NSAIDs and COX-2 inhibitors versus the known gastrointestinal benefits of COX-2 inhibitors.

Aspirin acetylates platelet membranes and irreversibly inhibits COX-1 mediated synthesis of thromboxane A2 (TXA2). Because platelets are anucleate and cannot regenerate COX-1 de novo, 95% inhibition of TXA2 completely inhibits platelet aggregation. By comparison, NSAIDs reversibly inhibit COX-1 in platelets; thus effects on platelet aggregation are dependent on the half-life of the agent. Aspirin showed protection against a first myocardial infarction in 22 071 men in the Physician’s Health Study. In 1013 postmenopausal women with myocardial infarctions documented in the UK General Practice Research Database, risk of a subsequent event was
significantly reduced with low-dose aspirin and unchanged with non-selective NSAIDs, compared with non-users. Six prospective, adequately powered trials13,14 and a meta-analysis15 of four epidemiological studies definitively showed that aspirin offers primary and secondary cardioprotection—and that non-selective NSAIDs do not. A dose–response for cardiovascular events with low-dose aspirin was also seen in a long-term study for prevention of recurrent colonic polyps.6

Cardiovascular risks of COX-2 inhibitors and non-selective NSAIDs

Randomised controlled trials

The US Food and Drug Administration (FDA) approved celecoxib in December, 1998, and rofecoxib in May, 1999. The VIGOR15 trial (panel) in 8076 patients with rheumatoid arthritis first raised concerns about the risk of acute cardiac events associated with rofecoxib. This drug was associated with fewer gastrointestinal ulcers and ulcer complications (eg, perforation, obstruction, or gastrointestinal bleeding), but with five times as many myocardial infarctions than was naproxen (table 1).16–30

Panel: Glossary of trial names

ADAPT: Alzheimer’s disease anti-inflammatory prevention trial
APC: Adenoma prevention with celecoxib
APPROVe: Adenomatous polyt prevention on vioxx
CLASS: Celecoxib in long-term arthritis safety study
MEDAL: Multinational etoricoxib and diclofenac arthritis long term
PreSAP: Prevention of spontaneous adenomatous polyps
SUCCESS: Successive celecoxib efficacy and safety study
TARGET: Therapeutic arthritis research and gastrointestinal event trial
VIGOR: Vioxx and gastrointestinal outcomes

<table>
<thead>
<tr>
<th>Panel: Glossary of trial names</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAPT: Alzheimer’s disease anti-inflammatory prevention trial</td>
</tr>
<tr>
<td>APC: Adenoma prevention with celecoxib</td>
</tr>
<tr>
<td>APPROVe: Adenomatous polyt prevention on vioxx</td>
</tr>
<tr>
<td>CLASS: Celecoxib in long-term arthritis safety study</td>
</tr>
<tr>
<td>MEDAL: Multinational etoricoxib and diclofenac arthritis long term</td>
</tr>
<tr>
<td>PreSAP: Prevention of spontaneous adenomatous polyps</td>
</tr>
<tr>
<td>SUCCESS: Successive celecoxib efficacy and safety study</td>
</tr>
<tr>
<td>TARGET: Therapeutic arthritis research and gastrointestinal event trial</td>
</tr>
<tr>
<td>VIGOR: Vioxx and gastrointestinal outcomes</td>
</tr>
</tbody>
</table>

Serious cardiovascular events were reported by investigators twice as frequently with rofecoxib, and in 321 patients (4%) with an indication for aspirin prophylaxis, all eight myocardial infarctions were in patients taking rofecoxib.31 Kaplan-Meier curves of the cardiovascular events in the treatment groups separated early (within 45–60 days) and remained different throughout the trial.30

Table: Cardiovascular risks of COX-2 inhibitors and non-selective NSAIDs

<table>
<thead>
<tr>
<th>Median duration (months)</th>
<th>Proportion of participants taking aspirin</th>
<th>Investigational drug group</th>
<th>Number of events</th>
<th>Number of events per 100 patient years</th>
<th>Comparator group</th>
<th>Number of events</th>
<th>Number of events per 100 patient years</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIGOR15,16</td>
<td>9</td>
<td>0%</td>
<td>Rofecoxib 50 mg once daily (n=4047)</td>
<td>45</td>
<td>1.67</td>
<td>Naproxen 500 mg twice daily (n=4029)</td>
<td>19</td>
<td>0.70</td>
</tr>
<tr>
<td>APTC analysis</td>
<td>Rofecoxib 50 mg once daily (n=4047)</td>
<td>64</td>
<td>2.37</td>
<td>Naproxen 500 mg twice daily (n=4029)</td>
<td>32</td>
<td>1.19</td>
<td>1.99†</td>
<td></td>
</tr>
<tr>
<td>APPROVe17,18</td>
<td>30</td>
<td>16%</td>
<td>Rofecoxib 25 mg once daily (n=1287)</td>
<td>46</td>
<td>1.50</td>
<td>Placebo (n=1299)</td>
<td>26</td>
<td>0.78</td>
</tr>
<tr>
<td>APTC analysis</td>
<td>Rofecoxib 25 mg once daily (n=1287)</td>
<td>34</td>
<td>1.11</td>
<td>Placebo (n=4029)</td>
<td>18</td>
<td>0.54</td>
<td>2.06 (1.16–3.64)*</td>
<td></td>
</tr>
<tr>
<td>MEDAL19,20</td>
<td>18</td>
<td>35%</td>
<td>Etoricoxib varying doses (n=16 819)</td>
<td>320</td>
<td>1.24</td>
<td>Diclofenac varying doses (n=16 483)</td>
<td>323</td>
<td>1.30</td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td>Etoricoxib varying doses (n=17 412)</td>
<td>495</td>
<td>1.25</td>
<td>Diclofenac varying doses (n=17 293)</td>
<td>468</td>
<td>1.19</td>
<td>1.05 (0.93–1.19)</td>
<td></td>
</tr>
<tr>
<td>APTC analysis</td>
<td>Etoricoxib varying doses (n=16 819)</td>
<td>216</td>
<td>0.84</td>
<td>Diclofenac varying doses (n=16 483)</td>
<td>216</td>
<td>0.87</td>
<td>0.96 (0.79–1.16)†</td>
<td></td>
</tr>
<tr>
<td>CLASS21,22</td>
<td>9</td>
<td>22%</td>
<td>Celecoxib 400 mg twice daily (n=3987)</td>
<td>34</td>
<td>1.50</td>
<td>Ibuprofen 800 mg three times daily (n=1985)</td>
<td>20</td>
<td>1.80</td>
</tr>
<tr>
<td>APTC analysis</td>
<td>Celecoxib 400 mg twice daily (n=3987)</td>
<td>52</td>
<td>2.24</td>
<td>Ibuprofen 800 mg three times daily (n=1985)</td>
<td>21</td>
<td>1.90</td>
<td>1.18†</td>
<td></td>
</tr>
<tr>
<td>Original analysis</td>
<td>Celecoxib 400 mg twice daily (n=3987)</td>
<td>34</td>
<td>1.5</td>
<td>Diclofenac 75 mg twice daily (n=1996)</td>
<td>15</td>
<td>1.40</td>
<td>1.07†</td>
<td></td>
</tr>
<tr>
<td>APTC analysis</td>
<td>Celecoxib 400 mg twice daily (n=3987)</td>
<td>52</td>
<td>2.24</td>
<td>Diclofenac 75 mg twice daily (n=1996)</td>
<td>28</td>
<td>2.60</td>
<td>0.86†</td>
<td></td>
</tr>
<tr>
<td>Original analysis</td>
<td>Celecoxib 400 mg twice daily (n=3987)</td>
<td>34</td>
<td>1.50</td>
<td>Combined NSAIDs (n=3981)</td>
<td>35</td>
<td>1.60</td>
<td>0.94†</td>
<td></td>
</tr>
<tr>
<td>APTC analysis</td>
<td>Celecoxib 400 mg twice daily (n=3987)</td>
<td>52</td>
<td>2.24</td>
<td>Combined NSAIDs (n=3981)</td>
<td>49</td>
<td>2.22</td>
<td>1.10 (0.70–1.60)</td>
<td></td>
</tr>
</tbody>
</table>

(Continues on next page)
These findings were interpreted as being due either to chance; to COX-2 selectivity, and therefore an imbalance in vascular endothelial effects versus platelet effects; or to cardioprotective effects of naproxen. A review of osteoarthritis trials included in rofecoxib’s approval application comparing rofecoxib 25 mg once daily (n=2785) with naproxen 500 mg twice daily (n=2771), in which 12·1–12·8% patients were on low-dose aspirin,
excess cardiovascular events occurred with rofecoxib in trials of only 12 weeks duration. The COX-2 selectivity hypothesis has subsequently been refuted as an explanation for cardiovascular events. In-vitro studies show that naproxen given twice daily inhibits platelet aggregation over 24 h, but they do not clarify whether this reversible effect is pharmacodynamically similar to irreversible inhibition of platelet TXA2 by aspirin. Cardiovascular events with rofecoxib in VIGOR were later recognised to be associated with a higher incidence of arrhythmias and more likely to be fatal than those with naproxen. Rofecoxib labelling was amended 14 months after approval to include potential cardiovascular risk. Rofecoxib was withdrawn from the market when the APPROVe trial in 2586 patients ended early in September, 2004, because of a two-fold increase in the number of cardiovascular events after treatment with rofecoxib 25 mg once daily compared with placebo (table 1) throughout the study.11–14

The FDA reviewed the VIGOR and CLASS studies at the same 2 day meeting in 2001. The latter enrolled 7968 patients with either rheumatoid arthritis (28%) or osteoarthritis. Patients were randomly assigned to receive either celecoxib 400 mg twice daily, ibuprofen 88 mg three-times daily, or diclofenac 75 mg twice daily. The CLASS study applied the Antiplatelet Trialists' Collaboration (APTC) definition of thromboembolic cardiovascular events (non-fatal myocardial infarction, non-fatal cerebrovascular accident, and sudden death, including transient ischaemic attacks).15 No significant differences were seen between treatment groups or in incidence of myocardial infarction. In December, 2004, the 3-year APC and PreSAP trials comparing celecoxib with placebo for reduction in recurrent colorectal polyps were stopped early because of significantly high numbers of cardiovascular events in the celecoxib 400 mg twice daily treatment group in APC (table 1).21–23 A combined risk analysis of both trials showed increased hazard ratios for adjudicated cardiovascular events with celecoxib 400 mg and 200 mg twice daily (table 1).24 In a prevention trial in Alzheimer’s disease (AD97-02-001) the number of APTC-defined cardiovascular events did not differ between treatment groups.25–28 It is difficult to interpret this result in view of the differences in cardiovascular risk factors and aspirin use at baseline.

None of the above trials were designed to assess the incidence of cardiovascular adverse events, and such analysis were initiated after the trials began. Although no large trials have been designed to assess the cardiovascular safety profile of valdecoxib and parecoxib, two trials evaluated their administration versus placebo for treatment of postoperative pain in patients undergoing coronary artery bypass graft surgery.29,30 Both showed excess cardiovascular events in the active treatment groups compared with placebo (table 1). These findings are difficult to generalise, having occurred in individuals with substantial vascular endothelial activation, placed on cardiac bypass pump, and on aspirin postoperatively, and events included intraoperative myocardial infarction that preceded administration of study drug. A combined analysis of trials for the valdecoxib new drug approval application included 7934 patients with rheumatoid arthritis or osteoarthritis independently adjudicated all acute cardiovascular events and showed similar crude and exposure-adjusted rates of events with valdecoxib, comparator NSAIDs, and placebo.31 Although no difference in the incidence of cardiovascular events was seen, data are limited both by number of patients and by differences in treatment exposure.

In the TARGET trial (panel) comparing lumiracoxib 400 mg once daily with naproxen 500 mg twice daily and ibuprofen 800 mg three times daily for 12 months in 18 325 patients with osteoarthritis, APTC endpoints did not differ statistically between lumiracoxib and non-selective NSAIDs. At FDA arthritis advisory committee meetings reviewing COX-2 inhibitors in February, 2005, Kaplan-Meier curves for each part of this study were presented, showing a numerically increased cardiovascular risk with lumiracoxib compared with naproxen but a decreased risk compared with ibuprofen.32 The FDA argued that results in the two lumiracoxib treatment groups were sufficiently different between the trials to preclude their combination into a single analysis, as was done for CLASS.

The cardiovascular safety profile of etoricoxib was recently assessed in three trials in the MEDAL programme in 34 701 patients with rheumatoid arthritis and osteoarthritis, 35% of whom were taking low-dose aspirin at baseline. The prespecified primary analysis was a comparison of etoricoxib 60 or 90 mg once daily with diclofenac 150 mg once daily on the basis of pooling cardiovascular events from all three trials. In the per-protocol population, no significant differences were noted in the incidence of confirmed cardiovascular or APTC events between COX-2 and non-selective NSAID treatment groups.

The only trial to compare cardiovascular risk of a non-selective NSAID with placebo is the ADAPT trial, in which patients were randomised 1:1:1 to receive naproxen, celecoxib, or placebo for 3 years. Results from this prematurely ended trial are difficult to interpret; however, more APTC events and congestive heart failure occurred in the naproxen group than either celecoxib or placebo groups.

In a meta-analysis of 138 trials, Kearney and colleagues analysed risk of cardiovascular events with COX-2 inhibitors versus placebo and non-selective NSAIDs on the basis of indirect comparisons with placebo using a common comparator. The relative risks were increased significantly with rofecoxib, celecoxib, and diclofenac (37 trials), but not ibuprofen and naproxen (41 trials). Results in this and earlier meta-analyses were dominated by data from CLASS, VIGOR, and TARGET trials, which provided the largest sample sizes. This analysis
Epidemiological studies

Epidemiological studies support the differing relative risk profiles for COX-2 selective and non-selective NSAIDs seen in randomised trials. Comparisons of results across epidemiological studies should favour prospectively defined cohort studies, and consider the number of events per treatment group, especially when few events occur in small groups, yielding wide 95% CIs.

Accounting for patient-reported over-the-counter aspirin use is difficult, because such reporting is susceptible to recall bias. In a meta-analysis of cohort and case-control studies, Hernandez-Diaz and colleagues found increased relative risks of acute myocardial infarction associated with diclofenac and rofecoxib at all doses and a suggestion of increased risk with ibuprofen. Another meta-analysis of 23 case-control and cohort studies by McGettigan and colleagues compared cardiovascular risks in a total of 537 332 patients and 112270 controls (table 2). Rofecoxib (at doses of 25 mg or less, or greater than 25 mg once daily) was associated with increased cardiovascular risk in the first 30 days of use, by contrast, celecoxib doses of up to 200 mg once daily were not; data were not sufficient to confirm a dose-dependent effect. These results were in accord with an increased cardiovascular risk with diclofenac noted in previous meta-analyses; an early risk of cardiovascular increased cardiovascular risk with celecoxib at doses of up to 200 mg once daily; but disputed that naproxen offered cardioprotection.

In a national hospital discharge registry in Finland of 33 309 individuals with first myocardial infarction and 138 949 matched controls, increased risks were associated with current use of all non-selective NSAIDs, partly selective, and COX-2 selective inhibitors including etoricoxib and valdecoxib. Solomon and colleagues compared cardiovascular risks in a total of 537 332 patients and 112270 controls (table 2). Rofecoxib (at doses of 25 mg or less, or greater than 25 mg once daily) was associated with increased cardiovascular risk in the first 30 days of use, by contrast, celecoxib doses of up to 200 mg once daily were not; data were not sufficient to confirm a dose-dependent effect. These results were in accord with an increased cardiovascular risk with diclofenac noted in previous meta-analyses; an early risk of cardiovascular increased cardiovascular risk with celecoxib at doses of up to 200 mg once daily; but disputed that naproxen offered cardioprotection.

In a national hospital discharge registry in Finland of 33 309 individuals with first myocardial infarction and 138 949 matched controls, increased risks were associated with current use of all non-selective NSAIDs, partly selective, and COX-2 selective inhibitors including etoricoxib and valdecoxib. Solomon and colleagues compared cardiovascular risks in a total of 537 332 patients and 112270 controls (table 2). Rofecoxib (at doses of 25 mg or less, or greater than 25 mg once daily) was associated with increased cardiovascular risk in the first 30 days of use, by contrast, celecoxib doses of up to 200 mg once daily were not; data were not sufficient to confirm a dose-dependent effect. These results were in accord with an increased cardiovascular risk with diclofenac noted in previous meta-analyses; an early risk of cardiovascular increased cardiovascular risk with celecoxib at doses of up to 200 mg once daily; but disputed that naproxen offered cardioprotection.
case-control study compared hospital admissions for acute myocardial infarction or ischaemic cerebrovascular accident in 74848 high-risk new users versus non-users. As in earlier series; rofecoxib was associated with increased risk in the first 30 days of use; naproxen showed less risk than rofecoxib. In a nested case-control study in 486378 patients, Andersohn and colleagues reported an increased risk of acute myocardial infarction with rofecoxib compared with non-use of rofecoxib in the previous year.

Thus, in randomised trials, rofecoxib was associated with increased risk of cardiovascular events in all but one trial; celecoxib showed increased risk in one trial with twice daily dosing. Results with lumiracoxib were different when compared with naproxen or ibuprofen. Importantly no trial was of sufficient size to definitely corroborate or rule out cardiovascular risk. In MEDAL, the only trial with an adequate sample size for analysis of cardiovascular events, etoricoxib did not differ significantly from diclofenac. All but three epidemiological studies have shown an increased risk of cardiovascular events with rofecoxib evident in trials, within 30 days of starting treatment. Single cohort and case-control studies show increased risk with celecoxib at doses higher than 200 mg once daily, consistent with findings in the 400 mg twice daily treatment group in APC, but this result was not seen in a meta-analysis of 31 trials by Moore and colleagues. With the exception of ADAPT, data for cardiovascular risk with non-selective NSAIDs remain limited to epidemiological series showing increased risks with diclofenac, meloxicam, ibuprofen, naproxen (table 2), indomethacin, and sulindac (data not shown).

**Cardiovascular events**

The causation of acute cardiovascular events is multifactorial, and the relative risk of events is not constant over time. Individual variability, underlying risk factors, and changes in blood pressure, renal function, and concomitant therapy can contribute to their occurrence. NSAIDs are known to induce a 4–6 mm Hg increase in blood pressure in susceptible individuals, and may be associated with new-onset and recurrent hypertension, peripheral oedema, and renal dysfunction (figure 1). Compared with non-selective NSAIDs, no cardiovascular differences were evident with celecoxib at therapeutic or supratherapeutic doses. Changes in blood pressure were smaller with lumiracoxib than with non-selective NSAIDs in TARGET. In patients with osteoarthritis and type 2 diabetes and hypertension taking ACE inhibitors, the recommended doses of rofecoxib 25 mg and celecoxib 200 mg once daily were compared with naproxen 500 mg twice daily using ambulatory blood-pressure monitoring. At the primary endpoint (6 weeks) and 12 weeks follow-up, rofecoxib was associated with significant mean increases in blood pressure of 3–4 mm Hg compared with no change or decreases with celecoxib and naproxen.

In a meta-analysis of 19 trials, in a total of 45451 participants, Aw and colleagues compared weighted mean differences in systolic and diastolic blood pressure, relative risk for developing hypertension or clinically important blood pressure elevations, or both. COX-2 inhibitors were associated with estimated mean increases in systolic and diastolic blood pressure compared with placebo (3·85/1·06 mm Hg) and non-selective NSAIDs (2·83/1·34 mm Hg), largely attributable to rofecoxib use, with a significantly higher risk of increases in blood pressure versus celecoxib. Chang and colleagues’ meta-analysis of hypertension, peripheral oedema, and renal dysfunction in 114 trials with 116094 participants suggested significant heterogeneity of cardiovascular risk between COX-2 inhibitors, with no class effect. Rofecoxib was associated with dose-dependent increased risk of hypertension, peripheral oedema, and renal dysfunction (figure 1). Compared with controls, celecoxib and other agents were not associated with cardiovascular risk; although only a few trials with

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hypertension Relative Risk (CI)</th>
<th>Peripheral Oedema Relative Risk (CI)</th>
<th>Renal Dysfunction Relative Risk (CI)</th>
<th>Arrhythmia Relative Risk (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib</td>
<td>1·55 (1·29–1·85)*</td>
<td>1·43 (1·23–1·66)*</td>
<td>2·90 (1·07–7·88)*</td>
<td>0·84 (0·45–1·57)†</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>0·83 (0·71–0·97)†</td>
<td>1·09 (0·91–1·31)</td>
<td>0·61 (0·40–0·94)†</td>
<td>1·28 (0·88–1·46)</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>1·28 (0·88–1·84)</td>
<td>1·13 (0·88–1·46)</td>
<td>1·68 (1·00–2·85)</td>
<td>1·09 (0·91–1·31)</td>
</tr>
<tr>
<td>Lumiracoxib</td>
<td>0·94 (0·42–2·12)</td>
<td>1·31 (0·75–2·31)</td>
<td>0·75 (0·17–3·32)</td>
<td>0·78 (0·62–1·01)</td>
</tr>
</tbody>
</table>

*Significantly increased relative risk. †Significantly decreased relative risk.

**Figure 1:** Meta-analysis of randomised controlled trials by relative risk (95% CI) of adverse events (A) hypertension, (B) peripheral oedema, (C) renal dysfunction, and (D) arrhythmia.
drugs other than celecoxib or rofecoxib were available for analysis. Several studies\textsuperscript{45,46} suggest that celecoxib is associated with fewer adverse renal effects than non-selective NSAIDs, and could be protective against aspirin-induced changes in renal function.\textsuperscript{47,48} In this large meta-analysis, only rofecoxib was associated with increased risk of non-fatal arrhythmia compared with placebo or active controls, with few events overall, and the sensitivity analysis was robust.

The differences in cardiovascular risk factors between rofecoxib and celecoxib might be explained by differences in structure, COX-2 selectivity, active metabolites, or mechanism of action. A 2-week crossover trial of celecoxib 200 mg twice daily assessed vascular endothelial function in 14 male patients with severe coronary artery disease and stable angina on aspirin and statins.\textsuperscript{49} Celecoxib treatment resulted in improved unstimulated vascular endothelial function and lower C-reactive protein concentrations than did placebo. In a similar small study over 1 week in 29 individuals with hypertension, celecoxib 200 mg twice daily improved flow-mediated dilatation and lower urinary levels of prostacyclin metabolites compared with placebo.\textsuperscript{50} By comparison, in two studies in patients with known coronary artery disease, administration of rofecoxib for 2–6 months was not associated with changes in flow-mediated dilatation.\textsuperscript{51,52}

Rofecoxib and celecoxib show different effects on cell-membrane integrity, which could explain the differing cardiovascular safety profiles for these drugs.\textsuperscript{53,54} Radiographical diffraction analyses suggest that rofecoxib changes the structure of cell-surface lipid molecules, thereby promoting oxidation of low-density lipoproteins and reducing the antioxidant capacity of plasma.

**Does low-dose aspirin protect against cardiovascular events associated with non-selective NSAIDs and COX-2 inhibitors?**

Data from trials of COX-2 inhibitors do not show whether or not low-dose aspirin is cardioprotective, because the numbers of participants are small and those taking aspirin have higher cardiovascular risk than individuals who do not. In a cohort study of 1.9 million patients in the California MediCal/Medicare system, with more than 7 million patient-years of exposure, 15.343 cases of acute myocardial infarction were matched with four nested case controls totalling 61370 (figure 2).\textsuperscript{99,100} Concomitant aspirin decreased risk of cardiovascular events when given with rofecoxib, celecoxib, indometacin, and meloxicam but not when given with ibuprofen.

Catella-Lawson and colleagues\textsuperscript{101} first showed that ibuprofen inhibited the beneficial effects of irreversible aspirin inhibition of TXA2 synthesis in platelets, by measuring concentrations of serum TXB2. Ibuprofen given before aspirin blocked access to binding serine 530 in the hydrophobic channel of platelet COX-1, which is probably true for all NSAIDs, except possibly diclofenac, which binds from the bottom up.\textsuperscript{102} By comparison, because of naproxen’s long half-life, whether or not it might be cardioprotective is unclear, especially when taken regularly at high doses. Capone and colleagues\textsuperscript{103} subsequently documented a pharmacodynamic interaction between naproxen and aspirin coadministration resulting in time-dependent inhibition of platelet aggregation. This pharmacodynamic interaction has clinically meaningful consequences with differential rates of myocardial infarction in ibuprofen plus aspirin users in both CLASS\textsuperscript{104} and TARGET\textsuperscript{105} trials and three epidemiological series,\textsuperscript{106,107,108} despite a meta-analysis to the contrary.\textsuperscript{109} The FDA issued a warning in September, 2006, against the use of ibuprofen with aspirin.\textsuperscript{109} As expected, coadministration of rofecoxib or celecoxib does not interfere with aspirin inhibition of platelet COX-1 activity.\textsuperscript{102,103}

Because of the potential interaction between non-selective NSAIDs and aspirin binding in the COX-1 pocket, aspirin should be given before the NSAID, or doses should be separated sufficiently according to half-life of the NSAID to allow aspirin entry. A large cohort

---

### Figure 2: Odds ratios (95% CI) for risk of acute myocardial infarction with COX-2 inhibitors and non-selective NSAIDs (A) and relative risk of cardiovascular events with COX-2 inhibitors and non-selective NSAIDs (B)

- **A**
  - Celecoxib, any dose
    - Odds ratio (95% CI): 1.09 (1.02-1.15)*
  - Rofecoxib, any dose
    - Odds ratio (95% CI): 1.32 (1.22-1.42)*
  - Ibuprofen
    - Odds ratio (95% CI): 1.11 (1.01-1.22)*
  - Naproxen
    - Odds ratio (95% CI): 1.08 (0.95-1.22)*

- **B**
  - Celecoxib, any dose
    - Odds ratio (95% CI): 1.12 (1.04-1.19)*
    - Odds ratio (95% CI): 0.88 (0.76-1.02)†
  - Rofecoxib, any dose
    - Odds ratio (95% CI): 1.31 (1.20-1.43)*
    - Odds ratio (95% CI): 1.03 (0.86-1.24)†
  - Meloxicam
    - Odds ratio (95% CI): 1.52 (1.14-2.03)*
    - Odds ratio (95% CI): 0.53 (0.26-1.10)†
  - Sulindac
    - Odds ratio (95% CI): 1.47 (1.03-2.11)*
    - Odds ratio (95% CI): 0.77 (0.32-1.85)†
  - Indometacin
    - Odds ratio (95% CI): 1.65 (1.27-2.15)*
    - Odds ratio (95% CI): 1.21 (0.66-2.27)†
  - Naproxen
    - Odds ratio (95% CI): 1.08 (0.97-1.19)
    - Odds ratio (95% CI): 1.20 (0.94-1.51)
study\textsuperscript{108} showed that concomitant aspirin reduced risk of cardiovascular events when given with rofecoxib, and abrogated risk with celecoxib, sulindac, meloxicam, and indometacin but not for ibuprofen.

**If low-dose aspirin is used as cardiovascular prophylaxis, are the gastrointestinal benefits associated with COX-2 inhibitors lost?**

If low-dose aspirin can decrease the incidence of acute cardiovascular events, is that benefit countered by an increased incidence of peptic ulcer bleeding? In a matched case-control series of patients aged older than 60 years with gastric or duodenal ulcer bleeding, Weil and co-workers\textsuperscript{116} showed that the gastrointestinal risk associated with 75–300 mg aspirin once daily was less than it was with non-selective NSAIDs, and was clearly exceeded by combination of the two. In regular aspirin users, a dose-response for risk of gastrointestinal effects was evident favoring 75 mg versus 150 mg versus 300 mg once daily. As with non-selective NSAIDs, gastrointestinal risk remains constant over time, even with enteric-coated aspirin.\textsuperscript{109,110} In a meta-analysis of 22 trials including patients taking aspirin for cardiovascular prophylaxis, aspirin in doses ranging from 75 mg to 325 mg increased the risk of major gastrointestinal and intracranial bleeding compared with placebo, irrespective of dose.\textsuperscript{111} Nonetheless, the absolute increases in risk were modest: 769 patients (95% CI 500–1250) would need to be treated with aspirin to cause one additional major bleeding episode a year.

Seven of the trials discussed previously enrolled patients on aspirin. In CLASS,\textsuperscript{10} the aspirin subgroup (21%) assigned to celecoxib had non-significant reductions in the numbers of symptomatic ulcers and ulcer complications.\textsuperscript{112} Celecoxib 400 mg twice daily with aspirin was associated at 6 months with significantly lower incidence (p<0.05) of clinically meaningful reductions in haematocrit (i.e., more than 10%) or haemoglobin (i.e., reduction of more than 20 g/L, 4.1% of participants) than with aspirin and ibuprofen (6.9%) or aspirin and diclofenac (7.5%).\textsuperscript{112} The SUCCESS-1\textsuperscript{10} (panel) study (n=8800) in osteoarthritis showed celecoxib 100 or 200 mg twice daily with aspirin to cause one additional major bleeding episode a year.

![Figure 3: Meta-analysis of celecoxib trials measuring endoscopically detected ulcers in (A) all patients, (B) patients taking aspirin, and (C) in patients not taking aspirin\textsuperscript{10} vs non-NSAID. *Significantly decreased relative risk.](image)

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion of patients with mucosal breaks</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1-week randomised controlled trial</strong>\textsuperscript{10}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib 200 mg twice daily (n=120)</td>
<td>16% (p=0.04)</td>
<td>0.63 (0.44–0.92)*</td>
</tr>
<tr>
<td>Naproxen 500 mg twice daily and omeprazole 20 mg once daily (n=118)</td>
<td>55% (p=0.001)</td>
<td>3.68 (1.79–7.60)†</td>
</tr>
<tr>
<td>Placebo (n=118)</td>
<td>7% (p=0.001)</td>
<td>2.62 (1.39–5.78)†</td>
</tr>
<tr>
<td><strong>2-week randomised controlled trial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib 200 mg twice daily (n=109)</td>
<td>6% (p=0.001)*</td>
<td>..</td>
</tr>
<tr>
<td>Ibuprofen 800 mg three times daily and omeprazole 20 mg once daily (n=112)</td>
<td>26% (p&lt;0.001)†</td>
<td>..</td>
</tr>
<tr>
<td>Placebo (n=113)</td>
<td>7% (p=0.77)†</td>
<td>..</td>
</tr>
</tbody>
</table>

*Celecoxib compared with NSAID. †NSAID and proton pump inhibitor compared with placebo. (Celecoxib compared with placebo.)

Table 3: Capsule endoscopy trials of celecoxib compared with non-selective NSAID and proton pump inhibitor or with placebo\textsuperscript{10,112}

In APPROVe,\textsuperscript{115} rofecoxib was associated with more ulcer complications than was placebo in both aspirin users (16%) and non-users. No trial was sufficiently powered to definitively assess gastrointestinal safety in these small populations of aspirin users. In the large MEDAL programme, significantly fewer uncomplicated upper
gastrointestinal events occurred in the 35% of individuals taking up to 100 mg aspirin and etoricoxib than in those on diclofenac and aspirin.136

In a meta-analysis of clinical reports from 31 trials comparing celecoxib with non-selective NSAIDs in osteoarthritis and rheumatoid arthritis, celecoxib was associated with significantly lower risk of endoscopically detected upper gastrointestinal ulcers than were non-selective NSAIDs, irrespective of aspirin use (figure 3).77 Number needed-to-treat to prevent one endoscopically detected ulcer was about seven, with or without aspirin use.

Proton-pump inhibitors reduce the production of gastric acid, but do not protect against gastrointestinal blood loss distal to the ligament of Treitz. Only use of COX-2 selective inhibitors protects against lower gastrointestinal blood loss, as shown in VIGOR9 with rofecoxib and in capsule endoscopy studies117,118 with celecoxib. Serious lower gastrointestinal events arose in 0·41 in 100 patient-years with rofecoxib compared with 0·89 with non-selective NSAIDs, which is a significantly smaller risk.139 In two capsule endoscopy trials of naproxen plus omeprazole for 1 week117 and ibuprofen plus omeprazole for 2 weeks138 with celecoxib or placebo, there were significantly fewer mucosal breaks in celecoxib treatment groups than with non-selective NSAIDs and proton-pump inhibitors (table 3). In the second trial,138 the percentage of participants with small bowel mucosal injury on celecoxib did not differ from placebo.

In a large trial130 1045 patients with osteoarthritis on aspirin 81 mg or 325 mg daily, received naproxen 500 mg twice daily and lansoprazole 30 mg once daily, or celecoxib 200 mg once daily, or placebo, with endoscopy at 12 weeks (table 4). The occurrence of gastroduodenal ulcers did not differ between the group on celecoxib and those on an non-selective NSAID and proton-pump inhibitor, irrespective of dose of aspirin. Two additional endoscopy studies assessed the occurrence of gastroduodenal ulcers in healthy volunteers assigned celecoxib or non-selective NSAIDs with either 325 mg or 81 mg aspirin (figure 4).131,132 Although more gastroduodenal ulcers were detected in the celecoxib group than in the placebo group, these ulcers were significantly fewer than those of the naproxen group in both trials, irrespective of dose of aspirin. Laine and colleagues131 studied patients with osteoarthritis aged older than 50 years assigned 81 mg enteric-coated aspirin alone or aspirin with rofecoxib 25 mg once daily, versus placebo, or ibuprofen 800 mg three times daily with endoscopies at 6 and 12 weeks. The groups on aspirin with rofecoxib and those taking ibuprofen had similar incidence rates of ulcers, which both significantly exceeded those of the placebo and aspirin only groups.

Table 4: Endoscopy trial comparing aspirin 325 mg or 81 mg once daily with celecoxib or non-selective NSAID and proton-pump inhibitor118

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Endoscopy trial comparing aspirin 325 mg or 81 mg once daily with celecoxib or non-selective NSAID and proton-pump inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib 200 mg once daily (n=426)</td>
<td>10% (p=0·64)*</td>
</tr>
<tr>
<td>Celecoxib 200 mg once daily and aspirin 325 mg (n=50)</td>
<td>12% (p=0·56)*</td>
</tr>
<tr>
<td>Celecoxib 200 mg once daily and aspirin 81 mg (n=176)</td>
<td>10% (p=0·44)*</td>
</tr>
<tr>
<td>Naproxen 500 mg twice daily and lansoprazole 30 mg once daily (n=428)</td>
<td>9%</td>
</tr>
<tr>
<td>Naproxen 500 mg twice daily and lansoprazole 30 mg once daily and aspirin 325 mg (n=45)</td>
<td>18%</td>
</tr>
<tr>
<td>Naproxen 500 mg twice daily and lansoprazole 30 mg once daily and aspirin 81 mg (n=383)</td>
<td>8%</td>
</tr>
</tbody>
</table>

* Celecoxib compared with NSAID.
However, this study did not compare aspirin with non-selective NSAID and proton-pump inhibitor.

In a hospital-based case-control study in Spain of 2777 consecutive patients with endoscopy-proven upper gastrointestinal bleeding and 5532 controls matched for age and sex without gastrointestinal bleeding or NSAID related events, non-selective NSAIDs were associated with highest risk of gastrointestinal bleeding, and rofecoxib or aspirin alone with an increased risk; however, no increased risk was evident with celecoxib, paracetamol, or non-selective NSAIDs with concomitant proton-pump inhibitor.124 Low-dose aspirin increased risk with both non-selective NSAIDs and COX-2 inhibitors—rofecoxib and celecoxib were not analysed separately because of the small number of events. In a large retrospective case-control study in Quebec, in a total of 791696 prescriptions, admissions for gastrointestinal perforation or haemorrhage in elderly patients taking prophylactic aspirin with non-selective NSAIDs or COX-2 inhibitors were compared (figure 5).125 Aspirin with either celecoxib or rofecoxib reduced adverse gastrointestinal events by about 50%, compared with non-selective NSAIDs and aspirin. Results were similar in a subsequent analysis of celecoxib alone.126

Together these data suggest that low-dose aspirin, especially up to 81 mg once daily, does not diminish the gastrointestinal benefits of COX-2 inhibitors over non-selective NSAIDs. Fewer people taking COX-2 inhibitors and aspirin had symptomatic ulcers and ulcer complications than those on non-selective NSAIDs and aspirin, but this difference was not significant in CLASS,18 SUCCESS,25 or TARGET.29 Significantly fewer uncomplicated upper gastrointestinal events occurred in the larger MEDAL.31–33 trial. Analysis of VIGOR31 and two capsule endoscopy studies172,173 show that COX-2 inhibitors resulted in significantly less distal gastrointestinal blood loss than did non-selective NSAIDs not protected against by use of proton-pump inhibitors. In two endoscopy studies,172,173 81 mg or 325 mg aspirin with celecoxib resulted in significantly fewer ulcers than did naproxen. In a large epidemiological cohort receiving doses of aspirin cited above, both celecoxib and rofecoxib reduced risk of admission for gastrointestinal adverse events.125,126

**If low-dose aspirin is used as cardiovascular prophylaxis, should COX-2 inhibitors rather than non-selective NSAIDs be given on the basis of relative gastrointestinal benefits and cardiovascular risk?**

Risk of gastrointestinal ulcers and ulcer complications with non-selective NSAIDs is 2–4%, is constant over time, and is evident as early as the first week of use.127–131 No evidence of tolerance exists and risk does not decrease over time with long-term use. On the basis of trials and meta-analyses, celecoxib, lumiracoxib, rofecoxib, and etoricoxib, are associated with significantly fewer symptomatic ulcers or complications, or both, than are non-selective NSAIDs. In a meta-analysis, Moore and co-workers18 showed similar gastrointestinal benefit of celecoxib, with or without aspirin. Although none of the earlier trials was sufficiently powered to definitively show gastrointestinal safety in aspirin users, the MEDAL programme showed significantly fewer uncomplicated upper gastrointestinal events with etoricoxib and aspirin. Further, Rahme and colleagues125 reported significantly fewer admissions for adverse gastrointestinal events with concomitant aspirin use with either rofecoxib or celecoxib, but not with non-selective NSAIDs. From the large simple trials designed to assess the gastrointestinal safety of COX-2 inhibitors versus non-selective NSAIDs, risk of symptomatic ulcers and ulcer complications was 2.1 per 100 patient years with rofecoxib versus 4.5 with naproxen; 0.67 with etoricoxib compared with 0.97 with diclofenac; 1.0–2.4 with celecoxib compared with 2.1–3.9 with combined non-selective NSAIDs in SUCCESS25 and CLASS;36 and 0.32 with lumiracoxib compared with 0.91 with combined non-selective NSAIDs; 1.06 with naproxen and 0.75 with ibuprofen.31,33,34,35,36

Data reviewed here do not clearly show a class effect for cardiovascular risk with COX-2 inhibitors, indicating that each agent should be considered individually in view of differences in dose, structure, pharmacokinetics, metabolism, and binding to cell-surface membranes. Furthermore, inclusion of exposure is crucial for estimation of cardiovascular risk. At up to 25 mg, rofecoxib will probably increase risk of cardiovascular events by 1.11–1.50 events per 100 patient years; at doses greater than 25 mg the risk increases within the first 30 days of use by 1.67–2.67 events per 100 patient years. By comparison, celecoxib has not been associated with risk at doses of up to 200 mg; doses greater than 200 mg show potential risk of 0.77–2.24 events per 100 patient years. Lumiracoxib (0.43–1.10 events per 100 patient years) might be associated and etoricoxib (1.24 events per 100 patient years) is associated with risk at high doses. Epidemiological data suggest that non-selective NSAIDs might increase cardiovascular risk as a class, although degrees of risk differ between specific agents and doses, and that naproxen might not be cardioprotective (combined NSAIDs 0.55–2.22 events per 100 patient years; ibuprofen 0.52–1.90; diclofenac 1.30–2.60; naproxen 0.57–1.19). Across these trials, event rates for placebo were 0.29–0.78 events per 100 patient years.

Although anti-inflammatory and analgesic effectiveness of NSAIDs and COX-2 inhibitors are similar, increased gastrointestinal tolerability and absence of pharmacodynamic interactions with aspirin suggest that use of low-dose aspirin with COX-2 inhibitors is preferable to non-selective NSAIDs with low-dose aspirin. In the California MediCal/Medicare study,34 concomitant low-dose aspirin reduced cardiovascular risk with rofecoxib, and diminished risk with celecoxib, sulindac, meloxicam, and indometacin but not with ibuprofen. Celecoxib and lumiracoxib have shown better tolerability...
in terms of hypertension, oedema and congestive heart failure than with comparator non-selective NSAIDs. Differences in FDA labelling for over-the-counter non-selective NSAID plus aspirin and celecoxib plus aspirin describing a pharmacodynamic interaction with NSAIDAs further support use of a COX-2 inhibitor with aspirin.11,12

Thus, comparison of the cardiovascular versus gastrointestinal risks is difficult to quantify: likelihood and severity differ between individuals, agents, and exposure. The 2–4% risk of gastrointestinal events over the first week, month, or year of use with non-selective NSAIDs exceeds the rates per 100 patient-years exposure for cardiovascular events cited above. However, the relative risk of cardiovascular events does not seem constant over time, and might be less with low doses of COX-2 inhibitors other than rofecoxib and non-selective NSAIDs (with the exception of naproxen). By contrast, the potential severity of gastrointestinal events will probably be much less than the clinical consequences of acute myocardial infarction, which accounts for most proven cardiovascular risk. In the largest case control series, California MediCal/Medicare, acute myocardial infarctions in a high-risk indigent population were associated with a mortality of 8%. Mortality associated with gastrointestinal events at about 0·08% is less than for myocardial infarctions.11 One could argue that this difference represents one in a hundred less risk of death, but could be complicated by the fact that gastrointestinal events could be asymptomatic, thereby potentially resulting in severe complications.

The data support the conclusion that COX-2 inhibitors are preferable to non-selective NSAIDs in patients with chronic pain and cardiovascular risk requiring low-dose aspirin, but relative risks and benefits should be assessed individually for each patient. The available COX-2 inhibitors, celecoxib, etoricoxib, and lumiracoxib, given in low doses with low-dose aspirin can provide the same pain and inflammatory relief as non-selective NSAIDs, with less gastrointestinal and cardiovascular risk. The concern that COX-2 inhibitors potentiated cardiovascular events has been informed by research and analysis, showing that risks differ between agents, and only with large doses of the available COX-2 inhibitors do such threats exist. Hopefully the data reviewed here will encourage further trials to directly address this important clinical quandary.

Conflict of interest statement
I have consulted for Abbott Immunology, Alexion, Amgen, Astellas, AstraZeneca, Bayhill, Biogen Idec, Bristol-Myers Squibb, CanFite, Cell Therapeutics, Centocor, Chelsea, Genentech, Cypress Biosciences, Dianipron Sumitomo, Entolos, Fibrogen, Genelabs, Genentech, Geron, GlaxoSmithKline, Human Genome Sciences, Icos, Immunomedics, Incyte, Lilly, La Jolla Pharmaceuticals, Millennium, Novartis, Omeros, Organon, Procter and Gamble, Robert Wood Johnson Pharmaceutical Research Institute, Pfizer, Pharmacia, Pharmacopeia, Proprius, Riget, Roche, Sanofi-Aventis, Schering-Plough, Scios, Serono, Seikagaku, UCB, Vertex, Wyeth Ayerst, Xdx and Xoma. I am on the advisory boards of Abbott, Amgen, Biogen Idec, Bristol-Myers Squibb, CanFite, Centocor, Chelsea, Novartis, Roche, Pfizer, Schering-Plough, and UCB. I serve on speakers bureaus of Abbott, Amgen, Centocor, and Pfizer. I have not and do not hold stock in any company. This Review was undertaken exclusively out of interest on my part, and I received no funding for its preparation.

Acknowledgments
I thank Jennifer Hansen-Feruch and Jack Loftis for their assistance in editing and formatting this manuscript and figures.

References
1. Smeets RJ, Wittink H, Hidding A, Knotterus JA. Do patients with chronic low back pain have a lower level of aerobic fitness than healthy controls?: are pain, disability, fear of injury, working status, or level of leisure time activity associated with the difference in aerobic fitness level? Spine 2006; 31: 90–97.


77 Johnson, A. NSAIDs and increased blood pressure. What is the clinical significance? Drug Safety 1997; 17: 277–89.


