Arthritis Research UK

Topical Reviews

An overview of current research and practice in rheumatic disease

Reports on the Rheumatic Diseases | Series 6 | **Spring 2010** | No 5

NSAIDs and coxibs

The stomach, the heart and the brain

Puja Mehta
Justin C Mason
Rheumatology and Cardiovascular Sciences, Bywaters Centre for Vascular Inflammation, Imperial College London, Hammersmith Hospital, London

- **Traditional non-steroidal anti-inflammatory drugs (tNSAIDs) and coxibs are effective analgesic, anti-inflammatory drugs**
- **Use of tNSAIDs and coxibs has been overshadowed by the withdrawal of rofecoxib**
- **tNSAIDs do not confer a reduced cardiovascular risk compared to coxibs**
- **tNSAIDs and coxibs are both associated with a small increase in cardiovascular events**
- **The relative cardiovascular and gastrointestinal risk must be assessed for each patient**
- **tNSAIDs and coxibs should be prescribed at the lowest effective dose and reviewed regularly**

Introduction

Traditional non-steroidal anti-inflammatory drugs (tNSAIDs) are effective analgesic and anti-inflammatory agents, which may be associated with gastrointestinal ulceration and bleeding, predominantly through inhibition of cyclo-oxygenase (COX)-1-mediated production of prostaglandins. Selective inhibitors of COX-2 (coxibs) were developed to minimise gastrointestinal toxicity while retaining analgesic and anti-inflammatory actions. However, since the withdrawal of rofecoxib (Vioxx) there has been widespread concern over potential cardiovascular toxicity and the risk of myocardial infarction (MI) and stroke associated with coxibs as compared to tNSAIDs. Key questions to inform therapeutic decision-making remain to be addressed, including: (i) What is the magnitude of the increased risk of cardiovascular events? (ii) Is this a class effect of the coxibs or do tNSAIDs impose a similar cardiotoxic profile? (iii) Does co-administration of aspirin minimise risk? (iv) How do we balance cardiovascular and gastrointestinal side-effects?

The cardiovascular controversy

The Vioxx Gastrointestinal Outcomes Research (VIGOR)[1] trial and the subsequent Adenomatous

Polyp Prevention of Vioxx (APPROVe)[2] study raised questions about the safety of rofecoxib, and the emphasis on adverse effects shifted away from gastrointestinal bleeding to thrombotic cardiovascular events. The VIGOR study compared rofecoxib 50 mg daily to naproxen 500 mg twice daily in 8076 patients with rheumatoid arthritis and demonstrated that while rofecoxib was associated with fewer severe adverse gastrointestinal events, there was a fivefold increase in atherothrombotic cardiovascular events, most notably MIs.[1] Cardiovascular events with rofecoxib in VIGOR were later recognised to be associated with a higher incidence of arrhythmias which were more likely to be fatal than those with naproxen.[1] The subsequent randomised placebo-controlled APPROVe trial, looking for the prevention of colon cancer recurrence in 2586 patients with adenomas, reported a twofold excess in thrombotic events after 18 months,[2] prompting worldwide withdrawal of rofecoxib. However, a subsequent comprehensive analysis of 114 double-blind randomised trials showed that although rofecoxib was associated with increased renal side-effects and a risk of cardiac arrhythmia, a class effect of the coxibs was not evident.[3]

Rofecoxib and cardiovascular disease: a class effect?

The debate continues as to whether the cardiovascular complications observed with rofecoxib are a specific feature of rofecoxib or a general class effect of the coxibs. Some studies have shown that other coxibs are associated with cardiovascular risk. A randomised trial reported that patients who received parecoxib and valdecoxib for postoperative pain in the first 10 days following coronary artery bypass grafting had a higher proportion of cardiovascular events during 30 days of follow-up compared with the placebo group.[4] These data are somewhat limited by the unique patient population, who may have had intra-operative MIs, were on aspirin post-operatively and were likely to have had significant endothelial activation by virtue of their placement on a cardiac bypass pump.[5] The safety review of the Adenoma Prevention with Celecoxib (APC) trial was terminated early because of an increase in cardiovascular events – 200 mg and 400 mg twice daily celecoxib carried a hazard ratio for cardiovascular mortality of 2.3 and 3.4 respectively compared to placebo.[6] Results of the APC trial provoked premature suspension of the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), which was designed to assess the use of naproxen 220 mg twice daily compared with celecoxib 200 mg twice daily for the primary prevention of Alzheimer dementia in 2528 patients.[7] Importantly, the ADAPT data did not show the same level of risk for celecoxib as seen in the APC trial and the data for naproxen suggested an increased cardiovascular and cerebrovascular risk.[7] The composite end point risk for MI, stroke or cardiovascular death over 3 years was 3.26% for celecoxib, 4.54% for naproxen and 3.74% for placebo (hazard ratios naproxen 1.57, celecoxib 1.14).[7] However, the reliability of these findings is questionable, as unfortunately the study was terminated early and there were differences in baseline cardiovascular risk factors and aspirin use.

Other trials argue against a class effect of coxibs on the cardiovascular system. The Celecoxib Long-term Arthritis Safety Study (CLASS) enrolled 7968 patients with either rheumatoid arthritis (28%) or osteoarthritis and evaluated the incidence of thromboembolic events in patients randomised to celecoxib 400 mg twice daily compared either with ibuprofen 800 mg three times daily or with diclofenac 75 mg twice daily.[8,9] No significant difference was seen between celecoxib and either tNSAID, irrespective of prophylactic aspirin use.[9] Pooled analysis from three prospective trials in the Multinational Etoricoxib and Diclofenac Arthritis Long-term trial (MEDAL) programme indicated that there was no significant difference between etoricoxib and diclofenac for any cardiovascular outcome.[10] The number of thrombotic cardiovascular events for etoricoxib 60 mg or 90 mg once daily and diclofenac 150 mg once daily was 1.24 versus 1.30 per 100 patient-years respectively (hazard ratio 0.95).[10] The primary composite thrombotic cardiovascular end point was the first occurrence of MI, unstable angina, intracardiac thrombus, resuscitated cardiac arrest, ischaemic stroke, transient ischaemic attack, pulmonary embolism and peripheral venous or arterial thrombosis.[10] The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) compared 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.[11] There was increased cardiovascular risk observed with lumiracoxib compared with naproxen, but decreased risk compared with ibuprofen.[12] The primary composite end point was cardiovascular mortality, non-fatal MI and stroke at

1 year; a secondary end point was the development of congestive cardiac failure.[12]

Differences between rofecoxib and celecoxib may be explained by differences in chemical structure, COX-2 selectivity, active metabolites, mechanism of action or different effects on cell membrane integrity.[5] A double-blind placebo-controlled 2-week crossover study using celecoxib 200 mg twice daily in 14 male patients with cardiovascular disease on aspirin and statins showed a beneficial effect of COX-2 inhibition compared with placebo.[13] This was assessed by analysis of flow-mediated dilatation (FMD), a means by which endothelial function can be explored in patients. An upper limb cuff is inflated to suprasystolic pressure for 5 minutes and the reactive hyperaemia which follows release, and reflects endogenous nitric oxide biosynthesis, is quantified by ultrasound analysis of brachial artery diameter. Celecoxib significantly improved FMD, and was associated with lower high-sensitivity C-reactive protein (CRP), although prostaglandin levels were unaffected.[13] In a similar study in 29 patients with hypertension, celecoxib 200 mg twice daily increased FMD,[14] while two studies using rofecoxib in patients with known cardiovascular disease did not show any positive change in FMD.[15,16]

These data suggest that significant differences exist between rofecoxib and celecoxib that may, at least in part, reflect COX-2-independent effects of celecoxib. For example, celecoxib, but not rofecoxib, inhibits tumour necrosis factor (TNF)α-induced tissue factor expression in endothelial cells via specific inhibition of c-jun terminal NH_2 kinase phosphorylation.[17] Subgroup analysis may identify patient characteristics that increase the cardiovascular risk and those agents prone to induce cardiovascular events,[18] and it has been suggested that, in contrast to rofecoxib, celecoxib at 200 mg/day is not associated with significant cardiovascular risk in patients with rheumatic diseases.[5,19]

Acute myocardial infarction and sudden cardiac death

A number of studies have evaluated the risk of acute MI, stroke and sudden cardiac death associated with coxibs and tNSAIDs. Findings of a retrospective cohort study suggested that, compared with controls, there was no increase in acute MI risk for new users of rofecoxib, celecoxib, naproxen and other tNSAIDs.[20] Other authors have challenged these data and suggest that rofecoxib, particularly at higher doses, confers an increased risk of acute MI. A case-control study in patients aged >65 years showed that current use of rofecoxib was associated with an elevated relative risk of acute MI compared with celecoxib (odds ratio 1.24) or in the absence of a tNSAID (odds ratio 1.14).[21] Doses of rofecoxib >25 mg/day were associated with a higher risk than doses of ≤25 mg/day.[21] This dose effect was supported by a retrospective cohort study that found that users of rofecoxib >25 mg/day were 1.70 times more likely than non-users to have coronary heart disease and among new users this rate increased to 1.93.[22] In contrast, there was no evidence of elevated risk among users of rofecoxib ≤25 mg/day or users of other tNSAIDs (ibuprofen and naproxen) or celecoxib.[22] Additionally, a cohort study that examined cardiovascular event rates in new users of coxibs and tNSAIDS found a significant elevation in the event rate for rofecoxib users (adjusted rate ratio 1.15), but not for other coxibs (celecoxib and valdecoxib) or tNSAIDs.[23]

The retrospective analysis performed by the Food and Drug Administration (FDA)[22] sought to determine the risk of acute MI and sudden cardiac death for patients taking tNSAIDs or coxibs. Current exposure to a coxib or tNSAID was compared with remote exposure to any tNSAID, and additionally rofecoxib was compared with celecoxib. Multivariate adjusted odds ratios versus celecoxib were: for rofecoxib (all doses) 1.59, for rofecoxib ≤25 mg/day 1.47 and for rofecoxib >25 mg/day 3.58. For naproxen versus remote NSAID use the adjusted odds ratio was 1.14. The authors concluded that rofecoxib increased the risk of serious coronary heart disease compared with celecoxib use and that naproxen was not cardioprotective.[22] However, the authors failed to emphasise the increased cardiovascular risk observed with naproxen and other tNSAIDs and the reduced risk associated with celecoxib observed in this study.

The coxibs are COX-1-sparing drugs

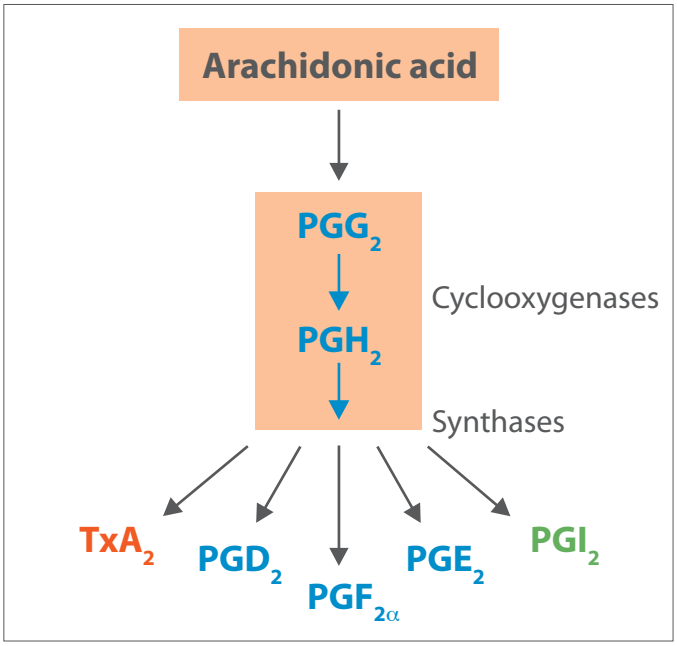
It is important to realise that all tNSAIDs and coxibs are used at doses that substantially inhibit COX-2 in order to provide the desired anti-pyretic, anti-inflammatory and analgesic benefits.[24] When used at therapeutic doses, the coxibs have very little effect on COX-1, in contrast to tNSAIDs. A recent review emphasised that a range of NSAIDs and coxibs provide 80% COX-2 inhibition, while COX-1

inhibition ranged from <10% for highly COX-2-selective inhibitors to >95% for some tNSAIDs.[24] Thus, the authors suggest that coxibs should correctly be termed 'COX-1-sparing drugs' in contrast to tNSAIDs. This COX-1-sparing property explains the reduction in gastrointestinal side-effects of coxibs as compared to tNSAIDs.

Mechanisms of cardiovascular risk

The mechanisms responsible for the increased cardiovascular risk associated with coxibs and tNSAIDs are not well understood and are likely to be multifactorial. It seems likely that relative levels of nitric oxide, prostacyclin (PGI_2) and thromboxane A_2 (TxA_2) will play an important role in endothelial homeostasis. Prostaglandins and TxA_2 are derived from arachidonic acid (Figure 1). PGH_2 is generated by the activity of cyclooxygenases from arachidonic acid via PGG_2. PGH_2 acts as the substrate for specific synthases, the products of which are TxA_2, PGI_2, PGD_2, PGE_2 and $PGF_{2\alpha}$ (Figure 1).

TxA_2 is a major COX-1-mediated product of arachidonic acid metabolism; it is synthesised primarily in platelets and promotes irreversible platelet aggregation, vasoconstriction and smooth muscle proliferation. Clinically, low-dose aspirin exerts its beneficial effects through irreversible



PG prostaglandin; Tx thromboxane

FIGURE 1. Derivation of prostaglandins from arachidonic acid. PGG_2 and PGH_2 are derived from arachidonic acid by the actions of cyclooxygenases. Specific synthases catalyse the conversion of PGH_2 into the prostanoids TxA_2, PGI_2, PGD_2, PGE_2 and $PGF_{2\alpha}$.

inhibition of COX-1 in platelets leading to reduced TxA_2 synthesis. In contrast, PGI_2 synthase expressed by endothelial cells generates PGI_2 from PGH_2. PGI_2 is a vasodilator, which inhibits platelet aggregation and smooth muscle proliferation.

The once-popular 'prostanoid hypothesis' refers to the role of PGI_2 and TxA_2 in vascular haemostasis. It suggested that coxibs were more likely to induce thrombotic complications because they would specifically inhibit PGI_2 synthesis and therefore distort the PGI_2:TxA_2 balance in favour of thrombosis. However, the 'prostanoid hypothesis' is now considered over-simplistic, not least because it fails to take into account the role of nitric oxide, and the fact that at standard doses tNSAIDs inhibit COX-2 at a similar level to coxibs.[24,25] Having said that, an alternative and credible mechanism for the cardiovascular side-effects of tNSAIDs and coxibs remains to be demonstrated.

tNSAIDs and coxibs dose-dependently reduce the urinary content of PGI_2 metabolites.[26-30] Since PGI_2 is an anti-thrombotic, anti-platelet hormone, reductions in its synthesis may increase platelet reactivity. tNSAIDs, but not coxibs, reduce urinary levels of TXA_2 metabolites,[26-30] suggesting reduced COX-1-mediated TXA_2 production in platelets. Platelet hyporeactivity may account for the gastrointestinal bleeding associated with tNSAID use. However, while aspirin inhibits COX-1 irreversibly and therefore bestows a sustained anti-thrombotic, anti-platelet effect, the anti-platelet protection of tNSAIDs is variable and dependent upon dose, frequency of use and half-life.[24] In practice, only naproxen has a significant platelet inhibitory effect and this is short-lived compared with aspirin.

Both coxibs and tNSAIDs may increase blood pressure in normotensive individuals and in those who have existing hypertension.[26-30] The TARGET study showed that at therapeutic doses congestive cardiac failure developed more often with ibuprofen than with lumiracoxib, but there was no significant difference between lumiracoxib and naproxen.[12] The study also showed that changes in blood pressure were smaller with lumiracoxib than with tNSAIDs.[12] Rofecoxib 25 mg once daily and celecoxib 200 mg once daily were compared with naproxen 500 mg twice daily in patients with hypertension, osteoarthritis and type 2 diabetes.[31] All three agents achieved similar efficacy in patients with osteoarthritis, while treatment with rofecoxib, but not celecoxib or naproxen, induced a significant increase in 24-hour systolic blood

pressure.[31] A meta-analysis of 19 trials suggested that coxibs were associated with elevated systolic and diastolic pressures compared with placebo and tNSAIDs, predominantly due to rofecoxib use, which induced a more significant rise in blood pressure than celecoxib.[32] An additional meta-analysis suggested that rofecoxib was associated with a dose-dependent increased risk of hypertension, peripheral oedema and renal dysfunction.[33] In clinical practice, rofecoxib and tNSAIDs, but not celecoxib, were shown to be associated with increased admission to hospital with congestive cardiac failure.[33]

COX-2 expression is induced during atherogenesis and may be detected in atherosclerotic plaques.[34] The effect of COX-2 inhibition on this process is not fully understood. For example the inhibitory effect on angiogenesis associated with coxibs[35] might be expected to reduce plaque growth, reduce the risk of intra-plaque haemorrhage and hence stabilise plaques. However, it has been reported that COX-2 inhibition may in fact play a role in destabilising atheromatous plaques.[36] Likewise, it is not clear whether the partial inhibition of COX-1 by various tNSAIDs compensates for any adverse cardiovascular effects of COX-2 inhibition.

Co-administration of aspirin: effect on cardiovascular and gastrointestinal risk

As yet we do not know whether co-administration of aspirin and a tNSAID or coxib is significantly cardioprotective.[5] There is some evidence to suggest that ibuprofen may distort the PGI_2:TxA_2 equilibrium by antagonising the cardioprotective effects of aspirin, through competition with aspirin for the COX-1 binding site on platelets.[37] In contrast, diclofenac, like many tNSAIDs and all coxibs, does not interfere with anti-platelet effects of low-dose aspirin.[37]

The clinical consequence of the interaction between ibuprofen and aspirin was reflected by different rates of MIs in patients taking both drugs in the CLASS[8] and TARGET trials.[12] The TARGET trial evaluated the effect of aspirin co-prescription and showed that in patients with osteoarthritis at high risk of thrombotic events, those taking aspirin had an increased cardiovascular event rate with lumiracoxib as compared to naproxen but a decreased risk as compared to ibuprofen.[12] In contrast, low-dose aspirin consumers treated with ibuprofen had a higher incidence of cardiovascular events than patients treated with lumiracoxib, a finding consistent with the hypothesis that ibuprofen interferes with the anti-platelet effects of aspirin.[12]

Perhaps of more direct clinical relevance, combined dosing of aspirin and tNSAIDs increases the risk of gastrointestinal haemorrhage and likewise co-prescribing aspirin and a coxib has a similar effect.[38] Current data suggest that low-dose aspirin may reduce the gastroprotective effects of coxibs. In the MEDAL programme, significantly fewer uncomplicated upper gastrointestinal events occurred in the 35% of individuals taking ≤100 mg aspirin and etoricoxib compared with those taking aspirin and diclofenac.[10] The use of proton-pump inhibitors (PPIs) has also been evaluated: analysis of VIGOR[1] and a capsule endoscopy study[39] showed that coxibs resulted in significantly decreased distal gastrointestinal blood loss compared with use of tNSAIDs (ibuprofen and naproxen) with PPIs. Furthermore, two endoscopy studies showed that in a population taking aspirin co-administration of celecoxib resulted in fewer gastroduodenal ulcers compared with naproxen.[40,41] In a large cohort of patients taking concomitant aspirin, there were significantly fewer admissions for adverse gastrointestinal events in those taking either rofecoxib or celecoxib, but not in those receiving tNSAIDs.[42] Of note the recent National Institute for Health and Clinical Excellence (NICE) osteoarthritis guidelines recommend co-prescription of PPIs with both tNSAIDs and coxibs (www.nice.org.uk/CG59). The failure of PPIs to protect against distal small bowel ulceration induced by tNSAIDs[39] merits further investigation and may influence prescribing decisions with regard to those considered to be at risk of gastrointestinal complications.

Coxibs and tNSAIDs increase cardiovascular risk

The current body of evidence suggests that both coxibs and tNSAIDs confer a small, significant and equivalent cardiovascular risk (Table 1), with celecoxib and naproxen possibly safer. Observational studies have provided most of the data associated with tNSAIDs; the only trial to compare the cardiovascular risks of a tNSAID with placebo is the ADAPT trial, in which patients were randomised to receive naproxen, celecoxib or placebo.[7] The results, although difficult to interpret, revealed more thromboembolic events and congestive cardiac failure in the naproxen group compared to either the celecoxib or placebo group.[7] In the

MEDAL trial, cardiovascular risks of etoricoxib did not differ significantly from diclofenac,[10] with 320 patients in the etoricoxib group and 323 in the diclofenac group suffering thrombotic cardiovascular events, yielding event rates of 1.24 and 1.30 respectively per 100 patient-years. Importantly, rates of upper gastrointestinal clinical events (perforation, bleeding, obstruction, ulcer) were significantly lower with etoricoxib than with diclofenac.[10]

TABLE 1. Relative risk of cardiovascular events.[19]
(Adapted with permission from McGettigan P and Henry D. JAMA 2006;296(13);1633-44. © 2006 American Medical Association. All rights reserved.)

Drug	Relative risk (95% confidence interval)
Rofecoxib all doses	1.35 (1.15–1.59)
Rofecoxib ≤25 mg/d	1.33 (1.00–1.79)
Rofecoxib >25 mg/d	2.19 (1.64–2.91)
Celecoxib all doses	1.06 (0.91–1.23)
Meloxicam	1.25 (1.00–1.55)
Diclofenac	1.40 (1.16–1.70)
Naproxen	0.97 (0.87–1.07)
Ibuprofen	1.07 (0.97–1.18)
Indometacin	1.30 (1.07–1.60)
Piroxicam	1.06 (0.70–1.59)

An observational study to determine the risks of MI in patients taking coxibs and tNSAIDs analysed data from 9218 cases with a first-ever diagnosis of MI over a 4-year study period.[43] A significantly increased risk of MI was observed with current use of rofecoxib, diclofenac and ibuprofen;[43] there was no significant increased risk with celecoxib and naproxen.[43] A cohort study used hospital discharge summaries of 2256 patients aged ≥66 years prescribed celecoxib, rofecoxib or tNSAIDs after an index admission for congestive cardiac failure.[44] The risk of death and recurrent congestive cardiac failure combined was higher in patients prescribed tNSAIDs or rofecoxib than in those prescribed celecoxib (hazard ratio 1.26 and 1.27 respectively).[44] Meanwhile, a meta-analysis of 138 trials reported that the relative risk of cardiovascular events was significantly increased with rofecoxib, celecoxib, diclofenac and ibuprofen, but not with naproxen.[45]

Epidemiological studies also support the finding of increased cardiovascular risk of tNSAIDs as well as coxibs. A systematic review of cohort and case-control studies[46] found increased relative risks of acute MI with ibuprofen, diclofenac and rofecoxib, but not with celecoxib or naproxen. A similar review found an increased cardiovascular risk with rofecoxib (dose-related) and diclofenac. Celecoxib was not associated with increased risk and naproxen was not found to be cardioprotective.[19]

Cardiovascular versus gastrointestinal risk

The risk of serious gastrointestinal complications of tNSAIDs has often been overlooked in the face of concern over cardiovascular risk, sometimes to the detriment of the patient. In patients with rheumatoid arthritis, tNSAID use is associated with a 1.58% incidence of hospital admission and 0.19% per year related risk of death due to gastrointestinal complications.[47] Although the initial VIGOR and CLASS trials demonstrated a significant gastrointestinal benefit of coxibs versus tNSAIDs, questions arose concerning the longevity of these benefits. Notwithstanding, subsequent large clinical trials have shown a significant decrease in upper gastrointestinal complications with coxibs, as compared with tNSAIDs;[1,11,48] however, concerns about atherothrombotic complications have overshadowed this favourable property of coxibs.

A recent study which collated data from meta-analyses to calculate annual event rates showed that gastrointestinal events occurred more frequently with tNSAIDs than with coxibs, while serious cardiovascular events occurred at equal rates.[49] Thus in the overall comparison, for every 1000 patients treated with a coxib rather than a tNSAID there would be eight fewer complicated upper gastrointestinal events, but one or more fatal or non-fatal MI or stroke. However, it is important to note that results varied between different coxib–NSAID comparisons. For every 1000 patients treated for a year with celecoxib rather than a tNSAID there would be twelve fewer upper gastrointestinal complications, and two fewer fatal or non-fatal heart attacks or strokes. For rofecoxib there would be six fewer upper gastrointestinal complications, but three more fatal or non-fatal heart attacks or strokes. These data reinforce the differences between coxibs and the need to select the most appropriate coxib or tNSAID for each individual patient.

No clear guidelines exist as regards when to co-prescribe a gastroprotective agent with tNSAIDs or coxibs (Table 2). However, as noted above recent NICE guidelines recommend co-prescription of a PPI with both in patients with osteoarthritis. Data from the Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-

TABLE 2. Cardiovascular versus gastrointestinal risk.

• Co-prescription of a PPI reduces the risk of GI events for tNSAIDs and coxibs
• Patients with CV risk on aspirin:
– avoid tNSAIDs or coxibs if possible
– if essential consider naproxen + PPI if GI risk low or coxib if significant GI risk
• CV risk varies between individual tNSAIDs and coxibs
• Risk of a CV event with tNSAID or coxib <1% in those with <2 risk factors
• Risk of a CV event may increase in the elderly, men, pre-existing CV disease
• Aspirin use increases the risk of GI events associated with tNSAIDs and coxibs
• GI risk varies between individual tNSAIDs
• PPIs are more effective than H_2 antagonists or misoprostol for gastroprotection

There remains a lack of randomised clinical trial data to assist with prescribing decisions and this is particularly so for those with pre-existing cardiovascular or gastrointestinal disease. The American College of Rheumatology White Paper provides a comprehensive review of current thinking.[25]

CV cardiovascular; GI gastrointestinal; tNSAID traditional non-steroidal anti-inflammatory drug; PPI proton-pump inhibitor

Associated Ulcer Treatment (ASTRONAUT) and Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) trials suggest that omeprazole is more effective than either ranitidine or misoprostol in this setting.[50,51] Further data concerning the potential long-term side-effects of PPIs are awaited with interest and may influence this choice in due course.

Coxibs, tNSAIDs and renal function

Initially it was hoped that the coxibs might be less prone to induce disturbances in renal function than tNSAIDs. However, it transpired that COX-2 is constitutively expressed in the kidney and that therapy with both coxibs and tNSAIDs is prone to lead to deteriorating renal function in susceptible patients. In those with a glomerular filtration rate (GFR) of <30 ml/min, coxibs and tNSAIDs should be avoided; if the GFR is between 30 and 60 ml/min they should be used with caution. It is important to use the GFR for treatment decisions rather than the serum creatinine level, and the former can be calculated using the Cockcroft–Gault formula.[52]

Summary of current perspective

The concern regarding the cardiovascular complications of tNSAIDs and coxibs has led to more considered prescribing, with physicians frequently recommending that these drugs be taken as required, rather than as a routine daily dose. However, downsides have included the use of tNSAIDs in place of coxibs on the basis of a perceived improved cardiovascular profile occasionally exposing susceptible patients to unnecessary gastrointestinal side-effects, or denial of anti-inflammatory drugs to those with inflammatory arthritis who might benefit significantly. Recent evidence suggests that there is no evidence for a class effect of coxibs with regard to cardiovascular risk.[10,12] Rofecoxib seems to confer a specifically high risk, and it has been calculated that for doses ≤25 mg daily the risk of cardiovascular events may be increased by 1.11–1.50 events per 100 patient-years, while at doses >25 mg the risk increases within the first 30 days of use by 1.67–2.37 events per 100 patient-years.[5] Furthermore, there does not appear to be a significantly increased cardiovascular risk associated with celecoxib ≤200 mg once daily[5,19,22] (Table 1). Doses of celecoxib >200 mg daily may exhibit a potential risk of 0.77–2.24 events per 100 patient-years.[5] The risk associated with tNSAIDs is limited to epidemiological data, and varies according to the tNSAID used,[5,19,22] with naproxen possibly representing the safest option in terms of cardiovascular risk and ibuprofen as regards gastrointestinal risk. However, it is important to remember that there is no randomised controlled trial data demonstrating that naproxen is effective in preventing cardiovascular events. Finally, where possible the use of coxibs and tNSAIDs should be avoided in patients requiring treatment with aspirin for cardiovascular disease. However, in those with chronic severe pain in whom treatment is required, low-dose coxibs are preferable to tNSAIDs.[5]

Clinical decision-making

The thrombogenic potential of anti-inflammatory agents is of great public interest, as many patients with arthritis are elderly with a high incidence of co-morbidities (hypertension, atherosclerosis, diabetes and dyslipidaemia), placing them at high

TABLE 3. tNSAID and coxib treatment guidelines.

• Prescribe the lowest effective dose for the shortest period of time
• Chronic pain: consider as required dosing only and review regularly
• Advise patient regarding potential toxicities
• Arrange appropriate monitoring: renal function, BP, liver function
• Patients on aspirin: avoid tNSAIDs and coxibs where possible
• Renal insufficiency: avoid where possible and in those with GFR <30 ml/min
• Hepatic insufficiency: avoid where possible and diclofenac in particular
• Anti-coagulation: avoid tNSAIDs in patients on warfarin or heparin
• NICE advises co-prescription of PPI with tNSAIDs and coxibs in osteoarthritis

BP blood pressure; GFR glomerular filtration rate; NICE National Institute for Health and Clinical Excellence; PPI proton-pump inhibitor; tNSAID traditional non-steroidal anti-inflammatory drug

cardiovascular risk. When deciding which anti-inflammatory agent to prescribe, clinicians should evaluate the risk of thrombotic cardiovascular events and gastrointestinal complications (bleeding and dyspepsia) as well as renovascular effects and congestive cardiac failure (hypertension and fluid accumulation) (Table 3). It is important to emphasise that tNSAIDs and coxibs do not differ in their ability to inhibit COX-2 and therefore we must safeguard against the prevalent belief that tNSAIDs carry a lower cardiovascular risk than coxibs. Both tNSAIDs and coxibs remain a viable and effective option to treat chronic pain and have a manageable cardiovascular safety profile; however, we must exercise caution in patients at high risk of both cardiovascular and gastrointestinal toxicity. The results of ongoing studies aimed at facilitating clinical decision-making, such as the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial,[53] are awaited with interest.

References

1. Bombardier C, Laine L, Reicin A et al; VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000;343(21):1520-8.

2. Bresalier RS, Sandler RS, Quan H et al; Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352(11):1092-102.

3. Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. JAMA 2006;296(13):1619-32.

4. Nussmeier NA, Whelton AA, Brown MT et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005;352(11):1081-91.

5. Strand V. Are COX-2 inhibitors preferable to non-selective non-steroidal anti-inflammatory drugs in patients with risk of cardiovascular events taking low-dose aspirin? Lancet 2007;370(9605):2138-51.

6. Solomon SD, McMurray JJ, Pfeffer MA et al; Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352(11):1071-80.

7. ADAPT Research Group. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). PLoS Clin Trials 2006;1(7):e33.

8. Silverstein FE, Faich G, Goldstein JL et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. JAMA 2000;284(10):1247-55.

9. White WB, Faich G, Whelton A et al. Comparison of thromboembolic events in patients treated with celecoxib, a cyclooxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. Am J Cardiol 2002;89(4):425-30.

10. Cannon CP, Curtis SP, FitzGerald GA et al; MEDAL Steering Committee. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 2006;368(9549):1771-81.

11. Farkouh ME, Kirshner H, Harrington RA et al; TARGET Study Group. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet 2004;364(9435):675-84.

12. Farkouh ME, Greenberg JD, Jeger RV et al. Cardiovascular outcomes in high risk patients with osteoarthritis treated with ibuprofen, naproxen or lumiracoxib. Ann Rheum Dis 2007;66(6):764-70.

13. Chenevard R, Hurlimann D, Bechir M et al. Selective COX-2 inhibition improves endothelial function in coronary artery disease. Circulation 2003;107(3):405-9.

14. Widlansky ME, Price DT, Gokce N et al. Short- and long-term COX-2 inhibition reverses endothelial dysfunction in patients with hypertension. Hypertension 2003;42(3):310-5.

15. Title LM, Giddens K, McInerney MM, McQueen MJ, Nassar BA. Effect of cyclooxygenase-2 inhibition with rofecoxib on endothelial dysfunction and inflammatory markers in patients with coronary artery disease. J Am Coll Cardiol 2003;42(10):1747-53.

16. Bogaty P, Brophy JM, Noel M et al. Impact of prolonged cyclooxygenase-2 inhibition on inflammatory markers and endothelial function in patients with ischemic heart disease and raised C-reactive protein: a randomized placebo-controlled study. Circulation 2004;110(8):934-9.

17. Steffel J, Hermann M, Greutert H et al. Celecoxib decreases endothelial tissue factor expression through inhibition of c-jun terminal NH_2 kinase phosphorylation. Circulation 2005;111(13):1685-9.

18. Solomon DH, Glynn RJ, Rothman KJ et al. Subgroup analyses to determine cardiovascular risk associated with nonsteroidal antiinflammatory drugs and coxibs in specific patient groups. Arthritis Rheum 2008;59(8):1097-104.

19. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclo-oxygenase 2. JAMA 2006;296(13):1633-44.

20. Mamdani M, Rochon P, Juurlink DN et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. Arch Intern Med 2003;163(4):481-6.

21. Solomon DH, Schneeweiss S, Glynn RJ et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004; 109(17):2068-73.

22. Graham DJ, Campen D, Hui R et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet 2005;365(9458):475-81.

23. Solomon DH, Avorn J, Sturmer T, Glynn RJ, Mogun H, Schneeweiss S. Cardiovascular outcomes in new users of coxibs and nonsteroidal antiinflammatory drugs: high-risk subgroups and time course of risk. Arthritis Rheum 2006; 54(5):1378-89.

24. Warner TD, Mitchell JA. COX-2 selectivity alone does not define the cardiovascular risks associated with non-steroidal anti-inflammatory drugs. Lancet 2008;371(9608):270-3.

25. American College of Rheumatology Ad Hoc Group on Use of Selective and Nonselective Nonsteroidal Anti-inflammatory Drugs. Recommendations for use of selective and nonselective nonsteroidal antiinflammatory drugs: an American College of Rheumatology White Paper [erratum in Arthritis Rheum 2008;59(11):1686]. Arthritis Rheum 2008;59(8):1058-73.

26. Antman EM, Bennett JS, Daugherty A et al. Use of non-steroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007;115(12):1634-42.

27. Grosser T. The pharmacology of selective inhibition of COX-2. Thromb Haemost 2006;96(4):393-400.

28. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. J Clin Invest 2006; 116(1):4-15.

29. Mitchell JA, Warner TD. COX isoforms in the cardiovascular system: understanding the activities of non-steroidal anti-inflammatory drugs. Nat Rev Drug Discov 2006;5(1):75-86.

30. White WB. Cardiovascular effects of the selective cyclo-oxygenase-2 inhibitors. Subcell Biochem 2007;42:145-58.

31. Sowers JR, White WB, Pitt B et al; Celecoxib Rofecoxib Efficacy and Study in Comorbidities Evaluation Trial (CRESCENT) Investigators. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. Arch Intern Med 2005;165(2):161-8.

32. Aw TJ, Haas SJ, Liew D, Krum H. Meta-analysis of cyclo-oxygenase-2 inhibitors and their effects on blood pressure. Arch Intern Med 2005;165(5):490-6.

33. Mamdani M, Juurlink DN, Lee DS et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. Lancet 2004;363(9423):1751-6.

34. Schonbeck U, Sukhova GK, Graber P, Coulter S, Libby P. Augmented expression of cyclooxygenase-2 in human atherosclerotic lesions. Am J Pathol 1999;155(4):1281-91.

35. Dannenberg AJ, Subbaramaiah K. Targeting cyclo-oxygenase-2 in human neoplasia: rationale and promise. Cancer Cell 2003;4(6):431-6.

36. Egan KM, Wang M, Fries S et al. Cyclooxygenases, thromboxane, and atherosclerosis: plaque destabilization by cyclooxygenase-2 inhibition combined with thromboxane receptor antagonism. Circulation 2005;111(3):334-42.

37. Catella-Lawson F, Reilly MP, Kapoor SC et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001;345(25):1809-17.

38. Lanas A, Garcia-Rodriguez LA, Arroyo MT et al; Asociacion Espanola de Gastroenterologia. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut 2006;55(12):1731-8.

39. Goldstein JL, Eisen GM, Lewis B, Gralnek IM, Zlotnick S, Fort JG; Investigators. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. Clin Gastroenterol Hepatol 2005;3(2):133-41.

40. Goldstein JL, Lowry SC, Lanza FL, Schwartz HI, Dodge WE. The impact of low-dose aspirin on endoscopic gastric and duodenal ulcer rates in users of a non-selective non-steroidal anti-inflammatory drug or a cyclo-oxygenase-2-selective inhibitor. Aliment Pharmacol Ther 2006;23(10): 1489-98.

41. Goldstein JL, Aisenberg J, Zakko SF, Berger MF, Dodge WE. Endoscopic ulcer rates in healthy subjects associated with use of aspirin (81 mg q.d.) alone or coadministered with celecoxib or naproxen: a randomized, 1-week trial. Dig Dis Sci 2008;53(3):647-56.

42. Rahme E, Barkun AN, Toubouti Y, Scalera A, Rochon S, Lelorier J. Do proton-pump inhibitors confer additional gastrointestinal protection in patients given celecoxib? Arthritis Rheum 2007;57(5):748-55.

43. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005;330(7504): 1366-9.

44. Hudson M, Richard H, Pilote L. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. BMJ 2005;330(7504):1370-3.

45. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 2006;332(7553):1302-8.

46. Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. Basic Clin Pharmacol Toxicol 2006; 98(3):266-74.

47. Fries JF, Williams CA, Bloch DA, Michel BA. Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models. Am J Med 1991;91(3):213-22.

48. Singh G, Fort JG, Goldstein JL et al; SUCCESS-1 Investigators. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-1 Study. Am J Med 2006;119(3): 255-66.

49. Moore RA, Derry S, McQuay HJ. Cyclo-oxygenase-2 selective inhibitors and nonsteroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk. BMC Musculoskelet Disord 2007;8:73.

50. Yeomans ND, Tulassay Z, Juhasz L et al; The Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1998;338(11):719-26.

51. Hawkey CJ, Karrasch JA, Szczepanski L et al; The Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1998; 338(11):727-34.

52. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

53. Becker MC, Wang TH, Wisniewski L et al; PRECISION Investigators. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal anti-inflammatory agents in patients with arthritis. Am Heart J 2009;157(4): 606-12.

Copeman House, St Mary's Court
St Mary's Gate, Chesterfield
Derbyshire S41 7TD

Tel 01246 558033 **Fax** 01246 558007
Email info@arthritisresearchuk.org
www.arthritisresearchuk.org

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Medical Editor: Andrew Keat. Production Editor: Frances Mawer.
ISSN 1759-7846. Published 3 times a year by Arthritis Research UK.