LEADING ARTICLE

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Balancing Gastroprotection and Cardioprotection with Selective Cyclo-Oxygenase-2 Inhibitors

Clinical Implications

Emma A. Meagher

Department of Medicine and Center for Experimental Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, USA

Abstract

NSAIDs have been the mainstay of treatment in the management of pain and inflammation associated with chronic inflammatory disorders. They are effective. However, complications arising from chronic NSAID use are common and are primarily due to gastrointestinal (GI) toxicity in the form of gastritis, peptic erosions and ulceration and GI bleeds. GI toxicity has been attributed to the blockade of the cyclo-oxygenase (COX)-1-mediated generation of the cytoprotective prostanoids, such as prostaglandin (PG) E_2 and PGI_2 (prostacyclin). More recently, selective COX-2 inhibitors ('coxibs') were designed to inhibit the production of COX-2-dependent inflammatory prostanoids and to leave intact the cytoprotective COX-1 products.

The coxibs, while exhibiting similar efficacy to traditional NSAIDs in controlled clinical trials of their efficacy in chronic inflammatory conditions, such as osteoarthritis and rheumatoid arthritis, have been associated with a reduced incidence of surrogate or actual indices of GI toxicity.

However, concerns regarding cardiovascular safety in high-risk patients have evolved. These concerns were driven initially by the concept that inhibition of COX-2-derived endothelial PGI_2 without concomitant inhibition of platelet thromboxane A_2 would result in increased cardiovascular risk. This was borne out in the Vioxx Gastrointestinal Outcomes Research study of rofecoxib, but not demonstrated in the Celecoxib Long Term Arthritis Safety Study trial.

Further elucidation of the relative roles of COX-1- and COX-2-generated prostanoids has enabled a greater understanding of the biology of these pathways. However, it is still not completely clear how this understanding may be appropriately translated into clinical medicine.

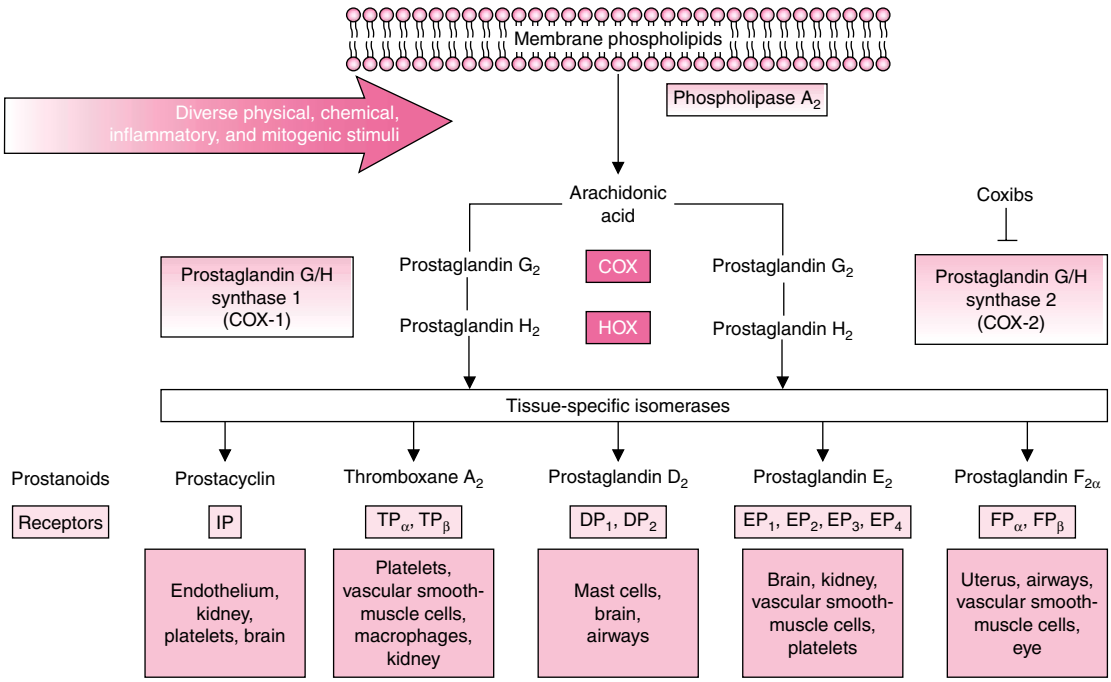

Fig. 1. Biosynthetic pathway of prostaglandins including enzymatic pathways, ligands and receptors subtypes inhibition (from FitzGerald and Patrono,[5] with permission from the Massachusetts Medical Society). **COX** = cyclo-oxygenase. **HOX** = hydroperoxidase.

NSAIDs are widely used to treat common conditions such as headache, fever, inflammation, dysmennorrhoea and joint pain. However, their efficacy is limited most commonly by adverse effects relating to the gastrointestinal (GI) tract. In particular, GI pain and dyspepsia are common complaints, but more serious complications, such as bleeding, can also occur less commonly. Thus, the introduction of selective cyclo-oxygenase (COX)-2 inhibitors ('coxibs') to the market in 1999 was welcomed.[1-3]

These drugs were developed on the basis of the theory that the anti-inflammatory and analgesic activity of NSAIDs was mediated primarily by inhibition of the COX-2-mediated production of inflammatory prostanoids, while the adverse GI effects were caused primarily by blockade of COX-1-mediated generation of cytoprotective prostanoids. Thus, selective COX-2 inhibitors presented physicians and patients alike with the opportunity to treat these common conditions with the expectation that GI toxicity would be minimal. Three years on, their cost effectiveness with respect to traditional NSAIDs has been questioned, and concerns have been raised relating to their cardiovascular safety.

This review will focus on the rationale underpinning the development of the coxibs, the translation of this knowledge into clinical practice and the evolution of concerns regarding their cardiovascular and renal profiles.

1. Physiological Function of Cyclo-Oxygenase (COX)

The prostaglandins (PGs) are a family of enzymatically produced products of arachidonic acid (AA).[4] They are generated by the activity of the COX enzyme that catalyses the transformation of AA into cyclic endoperoxide intermediates in a 2-step oxidation/reduction process that produces first PGG_2 then ultimately PGH_2 (figure 1). The

COX enzyme is a fatty acid dioxygenase; it is also less commonly known as prostaglandin G/H synthase.

Downstream of COX action, a range of synthases and isomerases further transform PGH_2 into different prostanoids including thromboxane A_2 (TxA_2), PGI_2 (prostacyclin), PGE_2, and $PGF_{2\alpha}$ (figure 1).

The expression of these synthases and the G protein coupled receptors which mediate prostanoid action varies between cells: usually cells produce one or two dominant products, accounting for the remarkably diverse spectrum of prostanoid action. Furthermore each prostanoid mediates different effects in different tissues. For example TxA_2, produced in platelets, induces platelet activation, vasoconstriction and smooth muscle cell proliferation. PGI_2, produced in endothelial cells, induces vasodilatation, inhibits platelet aggregation and smooth muscle cell proliferation. These two prostanoids play an essential role in the maintenance of vascular homeostasis. PGE_2 is produced in the kidney where it plays an important role in the regulation of renal blood flow and in salt and water homeostasis. In contrast this same PG confers cytoprotection in the GI epithelium.

1.1 COX Isoforms

Two isoforms of the COX enzyme, COX-1 and COX-2, have been identified, cloned and characterised.[6-8] Although they are somewhat similar in terms of protein structure (62% amino acid sequence homology) and activity they are subject to quite distinct patterns of regulated expression.[6] It was originally suggested that a clear distinction existed whereby COX-1 was constitutively expressed in tissues while COX-2 expression was induced in response to injury or inflammation. However, it is now recognised that COX-1 may also be upregulated in inflammation.[9,10] For example, both enzymes are co-expressed in inflamed synovium and in atherosclerotic plaques.[11,12] Similarly, COX-2 may be expressed constitutively in tissues such as kidney and brain. COX-2 may also be upregulated in endothelial cells by laminar shear *in vitro*[13] and the dominant contribution of COX-2 to PGI_2 formation in healthy humans suggests that this isoform may be constitutively induced in endothelial cells by haemodynamic forces *in vivo*.[14,15] However, COX-2 does seem to have emerged as the dominant (but not exclusive) source of PG formation in inflammation.[16] COX-1 is the only isoform present in mature human platelets, although COX-2 is expressed in the late phase of megakaryocyte maturation and has been detected in circulating immature platelets under conditions of accelerated platelet turnover.[17] In platelets, COX-1 converts AA into TxA_2. COX-1 is also the main isoform in the gastric epithelium, where it catalyses the formation of cytoprotective PGI_2 and PGE_2. Experiments in rodents suggest that COX-1 and COX-2 may interact in the issue of gastric cytoprotection. Thus, deletion of COX-1 alone does not result in gastric lesions in mice, whereas coincidental deletion of both COX isozymes does. It appears that COX-1 deletion or inhibition results in upregulation of COX-2 in gastric epithelium, which then contributes to cytoprotection.[18] Interestingly, clinical experience has shown that selective inhibition of COX-2 in humans reduces rather than abolishes GI toxicity seen with NSAIDs (see section 3).

2. COX Inhibitors

Three classes of COX inhibitors currently exist. They include traditional NSAIDs, selective COX-2 inhibitors and aspirin (acetylsalicylic acid). The coxibs are considered to be the first structural subclass of the selective COX-2 inhibitors (figure 2). Three of them – celecoxib, rofecoxib and valdecoxib – have been approved for use by the US FDA. One, parecoxib, the water-soluble prodrug of valdecoxib, has not yet successfully gained approval in the US, but it has been approved in the UK and

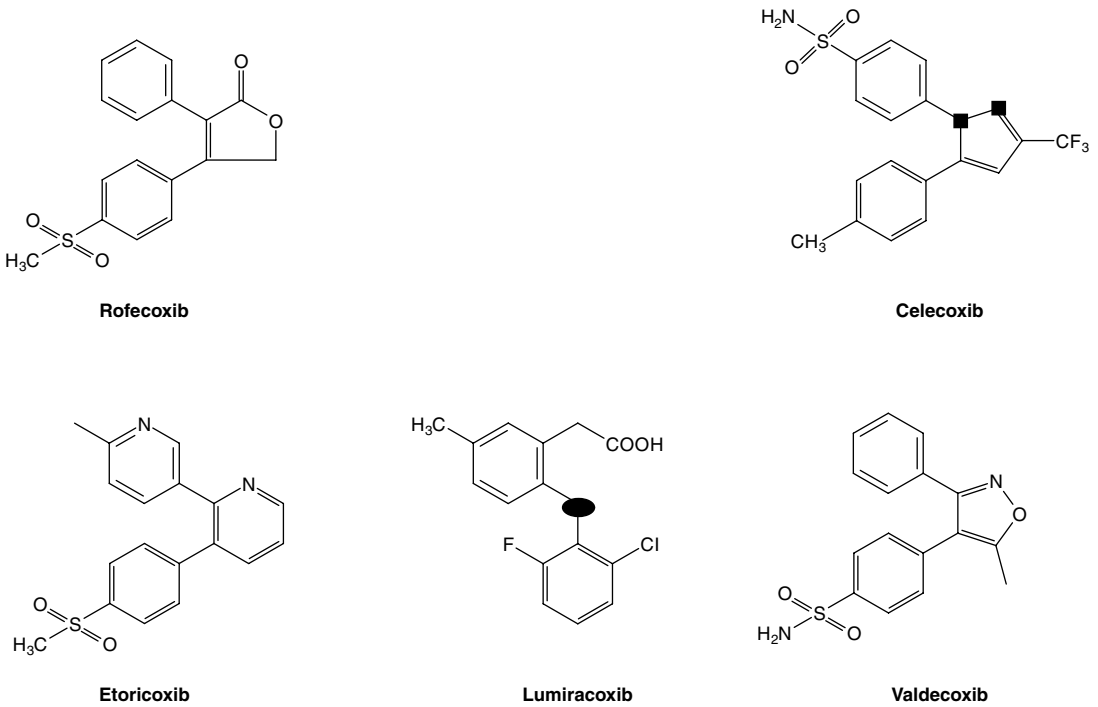

Fig. 2. Chemical structures of the coxibs. The coxibs are the first structural subclass of the selective cyclo-oxygenase-2 inhibitors. Of the five coxibs that have been studied, lumiracoxib is of a different structural class and is a structural analogue of diclofenac.

other European countries as an injectable formulation for the short-term treatment of postoperative pain. Etoricoxib has been recently approved in the UK and various other countries for the treatment of osteoarthritis, rheumatoid arthritis and acute gouty arthritis. In the US, the application for approval of etoricoxib was withdrawn before a decision was made by the US FDA, but the application is likely to be resubmitted in the future. Ongoing studies of these compounds are complimented by a large phase III study of lumiracoxib, a structural analogue of the traditional NSAID, diclofenac (figure 2).

2.1 Nonselective COX Inhibition

Aspirin induces irreversible covalent modification of both COX isoenzymes through irreversible acetylation of a serine residue at position 520. It is the only clinically relevant NSAID that covalently modifies COX. NSAIDs induce noncovalent modification of the enzyme that can be either reversible or irreversible through binding to the active site of the enzyme (figure 3). The GI toxicity of NSAIDs and aspirin has been attributed to the inhibition of COX-1 in GI epithelium, but may also involve inhibition of COX-2.[16,18] Other aspects of coincidental inhibition may offset each other. Thus NSAIDs and aspirin inhibit coincidentally COX-1-derived TxA_2 and COX-2-derived PGI_2. Theoretically, any thrombotic hazard that might derive from PGI_2 inhibition would be offset by the beneficial effects of preventing generation of TxA_2; thus the net effect of aspirin, even at high doses where both COX-1 and COX-2 are inhibited, is to prevent cardiovascular events in at-risk patients.

COX-2-derived PGI_2 and PGE_2 seem important in the maintenance of renal blood flow under renoprival conditions. COX-1-derived PGs, like TxA_2 and $PGF_{2\alpha}$, by contrast, reduce medullary blood

flow.[19] Thus, renovascular complications of NSAIDs due to COX-2 inhibition might be offset to some degree by coincidental inhibition of COX-1.[20]

Aspirin irreversibly acetylates a serine residue at position 530 in human platelet COX-1 enzyme.[21] This prevents access of AA to the catalytic site and results in permanent inactivation of the enzyme. The anucleate, mature platelet is not able to synthesise COX-1 *de novo* and it does not possess COX-2 activity. The net effect is a reduction in TxA_2 production that persists for the lifetime of the platelet: complete recovery depends on platelet turnover time, usually 12–14 days, although function is effectively restored (based on bleeding times) with ~10% capacity in 3–4 days. An oddity that relates to drug action is the nonlinear relationship between inhibition of COX-1-derived TxA_2 and TxA_2-dependent platelet activation.[22] Thus, >95% inhibition of enzyme capacity is required to inhibit function. In the case of most traditional NSAIDs, the inhibitory effect on TxA_2 falls below that required to block function early within a typical dosage interval and would thus not be expected to afford cardioprotection. By contrast, the prolonged irreversible inhibition of TxA_2 by aspirin produces sustained cardioprotection that allows every other day administration[23] and is sufficient to explain a reduction in the secondary incidence of heart attack and stroke.[24]

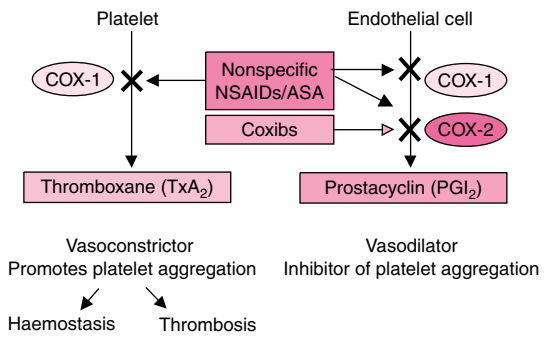

Fig. 3. Functional relevance of selective versus nonselective cyclooxygenase (COX)-2 inhibition. **ASA** = aspirin (acetylsalicylic acid).

Thus, although higher doses of aspirin (1000–1500 mg/day) coincidentally inhibit COX-1 and COX-2 and possess anti-inflammatory activity, indirect comparisons across controlled clinical trials suggest that the impact of higher dosages on secondary prevention is no greater (and perhaps somewhat less) than that of much lower doses targeted to the platelet.[24]

2.2 COX-2-Selective Inhibition

Coxibs are relatively selective for the COX-2 isoform. They differ in terms of their absolute selectivity for COX-2, based on *ex vivo*, whole blood assays of enzyme activity.[25-27] Celecoxib exhibits a selectivity similar to that of some older drugs, such as meloxicam and diclofenac in whole blood assays (figure 4).[27] Rofecoxib and valdecoxib are similarly selective to each other, but more so than celecoxib. Etoricoxib is the most selective of the coxibs to date. However, while these assays are extremely useful as a guide to drug development and dose finding, they are unproven as comparative surrogates for the efficacy of these compounds in inflammatory syndromes *in vivo*. Thus, we have no idea whether these observed differences in selectivity translate into differential efficacy or adverse event profiles in the absence of controlled, head-to-head comparisons. Such issues warrant investigation.

3. Clinical Assessment of COX-2-Selective Inhibitors

Given the rationale for the development of selective COX-2 inhibitors, it is perhaps unsurprising that their evaluation has been configured with a trial design that seeks a divergence in adverse effect profiles from regular NSAIDs when used at doses of similar therapeutic efficacy. However, it is timely to assess their relative clinical efficacy as a function of the degree of COX-2 inhibition and the selectivity with which it is attained. It will also be interesting to

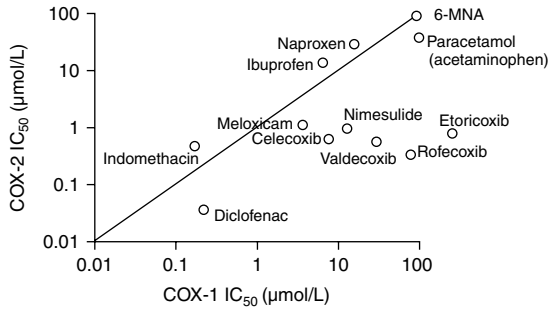

Fig. 4. Concentrations of various drugs required to inhibit activity of cyclo-oxygenase (COX)-1 and -2 by 50% (IC_{50}) in assays of whole blood (from FitzGerald and Patrono,[5] with permission of the Massachusetts Medical Society). **6-MNA** = 6-methoxy-2-naphthylacetic acid.

determine the respective duration of COX-1 and COX-2 inhibition with these compounds given that they are slow, tight-binding inhibitors of COX-2 and competitive inhibitors of COX-1.

Several studies have demonstrated the anti-inflammatory and/or analgesic efficacy of coxibs in conditions as diverse as dental pain, dysmennorrhoea and joint pain associated with rheumatoid arthritis and osteoarthritis.[28-33] Given the association of both aspirin and NSAID consumption with a reduced incidence of GI cancer [34,35] and progression of Alzheimer's disease[36-38] there is continuing interest in the potential role of selective COX-2 inhibitors in these conditions.[39,40]

Indeed, celecoxib has been shown to reduce the number of adenomatous polyps in patients with familial adenomatous polyposis coli.[41] The dose of celecoxib used in this particular study was 2-fold higher than the currently recommended dose for rheumatoid arthritis. In addition, the comparator was placebo rather than aspirin or a mixed inhibitor and it is unknown if these drugs represent a cheaper alternative. Both COX-2[42] and COX-1 deletion[43] have been shown to reduce the number of intestinal polyps in Apc mice, suggesting that the interplay between the enzymes and the comparative therapeutic utility of their inhibitors may prove to be complex.

3.1 Clinical Trials Addressing the COX-2 Hypothesis

The comparative effects of coxibs and NSAIDs on GI safety were evaluated in controlled studies using surrogate endpoints. Most commonly, the endpoints included endoscopic evaluation of gastroduodenal ulceration after 3–6 months of therapy. Cross-sectional endoscopic studies have shown that the combined prevalence of gastric and duodenal ulcers is 10–25% in patients with chronic arthritis treated with NSAIDs.[44] Almost without exception, coxibs have been associated with a markedly diminished hazard of developing such endpoints. In some cases, this was associated with a significant reduction in GI symptoms, when these were present. This was most apparent in the case of GI pain.[31,45-47]

While this promising profile was accepted by the US FDA as a basis for drug approval, the really important question for clinicians was whether this distinct profile would extend to the rarer, but more life-threatening hazard of GI ulcer perforation and bleeding. Two large clinical trials which address that question, the Celecoxib Long Term Arthritis Safety Study (CLASS)[48] and the Vioxx Gastrointestinal Outcomes Research (VIGOR),[49] involving celecoxib and rofecoxib, respectively, have been reported and a third, involving lumiracoxib, is underway.

3.1.1 The VIGOR (Rofecoxib) Study

The VIGOR study randomised 8076 patients with rheumatoid arthritis to receive therapeutically equivalent doses of oral rofecoxib (50mg daily) or naproxen (500mg twice daily) for 9 months in a double-blind randomised fashion.[49] The mean age of patients was 58 years and 80% were women. Concomitant glucocorticoid therapy was documented in 60% of participants and 8% had a significant past medical history of peptic ulcer disease as defined by a history or symptoms, haemorrhage or perforation. Use of aspirin was not allowed.

The incidence of pre-specified primary and secondary clinical endpoints reflecting ulceration and its complications were significantly reduced from 4% with naproxen to 2% with rofecoxib.[49] The primary endpoint of the study was confirmed clinical upper GI events, including symptomatic ulcers, upper GI bleeding, perforation and obstruction. The results demonstrated a 54% relative risk reduction in favour of rofecoxib. In absolute terms, 41 patients would need to be treated with rofecoxib instead of naproxen to avoid one clinical upper GI event in 1 year. Secondary endpoints also demonstrated significant results. Thus, the relative risk of complicated upper GI events including perforation, obstruction and severe bleeding with ≥2 g/dL decrease in haemoglobin levels was reduced by 57% and the relative risk of all clinical bleeding was reduced by 62%.

Naproxen and rofecoxib had similar efficacy in terms of management of pain in patients with rheumatoid arthritis. The discontinuation rate due to lack of efficacy was 6.3% in the rofecoxib group compared with 6.5% in the naproxen treated group.[49]

The authors' conclusion was that treatment with twice the standard rofecoxib dose in patients with rheumatoid arthritis led to a significant reduction in GI toxicity when compared with conventional naproxen therapy. Both drugs had similar efficacy with respect to control of symptoms of arthritis.

3.1.2 The CLASS (Celecoxib) Trial

The double-blind CLASS trial consisted of two separate arms.[48] In one, oral celecoxib (400mg twice daily) was compared with diclofenac (75mg twice daily) and in the other, the same dose of celecoxib was compared with ibuprofen (800mg three times daily). The dose of celecoxib used was 2–4 times the maximum effective and recommended dose for rheumatoid arthritis and osteoarthritis. Here, 8059 patients were recruited; 72% had osteoarthritis and 28% had rheumatoid arthritis. Sixty patients were taking corticosteroids and approximately 10% had a history of GI bleeding or ulceration at study entry. Patients were allowed to take aspirin for cardiovascular prophylaxis.

The study lasted 13 months. However, only the results from the first 6 months were reported initially and these data compared celecoxib with the combined, not individual, NSAIDs. A later analysis of both rofecoxib[50] and celecoxib[51] performed by the US FDA's Arthritis Advisory Committee was posted on the FDA website and subsequently reported and discussed in the literature.[52] This analysis included all the data from the CLASS trial and also subjected the data to appropriate analysis of the two separate NSAID arms, according to the predefined protocol.

The primary endpoint of the CLASS trial was the incidence of defined ulcer complications including bleeding, perforation and gastric outlet obstruction. The differences between the event rates with respect to the primary endpoint were not statistically significant for any comparison. The secondary endpoint included ulcer complications and symptomatic ulcers. The incidence of the secondary endpoint with celecoxib was significantly lower compared with ibuprofen, but did not differ significantly from diclofenac.[48]

3.1.3 Trial Results in Perspective

Thus, the outcome of the VIGOR study rejects the null hypothesis, sustaining the theoretical rationale that underpins the development of selective COX-2 inhibitors. CLASS, by contrast, failed in this objective. Oddly, this distinction has not impinged on the relative acceptance by the market of the two coxibs.

There were significant differences in the trial designs of VIGOR and the CLASS that deserve mention.

The first was in the definition of the pre-specified GI endpoints. A greater number of endoscopies were performed in CLASS; this unveiled a greater number of symptomatic ulcers than in VIGOR. In

the VIGOR trial, the definition of complicated ulcer was broader, with respect to GI bleeding. There was a larger drop-out rate in the CLASS trial: 40% withdrew from the celecoxib group, while 45% withdrew from the combined NSAID-treated group. The exact reasons for this discrepancy from VIGOR (29% withdrawal from both groups) are not clear.

A further difference was the use of aspirin by 21% of the study population in the CLASS study. Aspirin use was excluded from VIGOR. Inclusion of a substantial number of individuals taking aspirin could have modified both the incidence of GI events and the detection of cardiovascular events in the two studies. However, a formal analysis of the possibility of a statistical interaction between aspirin and celecoxib use was not possible in CLASS. A *post hoc* analysis suggested that aspirin use might obscure the differential impact of celecoxib and the NSAIDs on GI effects.[48] However, although this was reported in the original paper, the patients were not stratified for aspirin use *a priori* and the report was based on the incomplete GI data set.

3.2 Cardiovascular Outcomes

Additional to the GI outcomes, the VIGOR investigators were requested by the steering committee to incorporate cardiovascular outcomes as a prespecified endpoint in their trial design. This was based on the observation that both celecoxib and rofecoxib substantially depressed urinary excretion of a major PGI_2 metabolite, suggesting a reduction in endothelial biosynthesis of this vasodilator and platelet inhibitory prostanoid.[14,15] As this would be unaccompanied by concomitant inhibition of COX-1-derived TxA_2 by platelets, it might represent a mechanism by which coxibs could exert a cardiovascular hazard.

The outcome found in VIGOR was a significant, 5-fold divergence in the incidence of myocardial infarction between the rofecoxib (21 events) and naproxen groups (four events),[49] which has provoked much speculation.[52] A similar divergence in cardiovascular events was not observed in CLASS, as would have been expected if this was a complication reflecting a mechanism common to selective COX-2 inhibitors.

There are several potential explanations for the divergence in these findings. The finding may reflect the play of chance alone. There was a small absolute number of events. Two mechanistic explanations have been advanced; a cardiovascular hazard of coxibs or a cardioprotective effect of naproxen.

Whether selective depression of PGI_2 formation represents a cardiovascular hazard in humans is unknown. However biosynthesis of this PG is increased in syndromes of platelet activation and it has been suggested to function as a homeostatic response ligand when platelet vascular interactions are increased.[53] Furthermore, study of the response to vascular injury in receptor-deleted mice established that PGI_2 modulates the cardiovascular response to TxA_2 *in vivo*.[54]

If this was indeed the case in humans as well as in mice, why was a cardiovascular hazard not observed in CLASS? Firstly, cardiovascular outcomes were not pre-specified in CLASS and although they were subsequently counted, they were not adjudicated. Secondly, one-fifth of the patients in CLASS, perhaps those at greatest risk of a cardiovascular event, were on aspirin. This may have obscured – although not, theoretically, abolished – a cardiovascular signal. PGI_2 inhibits platelet activation by all known agonists, not just TxA_2. Deletion of the PGI_2 receptor does not result in spontaneous thrombosis. Rather, it enhances the response to thrombotic stimuli.[54] Thus, this mechanism would be anticipated to be operative only in patients at increased risk of thrombosis for other reasons. Finally, the clinical substrate may have been an important distinction between the trials. The VIGOR study enrolled only patients with rheumatoid arthritis. In contrast, 72% of the patients

studied in the CLASS trial had osteoarthritis with the remaining 28% having a diagnosis of rheumatoid arthritis. Retrospective epidemiological data suggest that the incidence of thrombotic events is increased in patients with rheumatoid arthritis compared with patients with osteoarthritis or the general population.[55-57] A more recent analysis of the General Practice Research Database (GPRD) showed that among 6.5 million patients with no prior history of stroke or myocardial infarction, those with rheumatoid arthritis had a 55% greater risk of a myocardial infarction than patients who did not have arthritis and a 32% greater risk than those with osteoarthritis.[58]

Indeed, consistent with the possible relevance of the clinical substrate, overview analyses of rofecoxib trials in patients at low cardiovascular risk have failed to detect a cardiovascular hazard,[59] while cardiovascular signals have emerged with structurally distinct inhibitors in populations potentially enriched with relevant patients. A study of parecoxib and valdecoxib revealed a clustering of cardiovascular events in the treated versus placebo control groups in patients undergoing cardiovascular bypass.[60] These results must be interpreted with caution as the sample size of the study (several hundred patients) was not adequate to assess cardiovascular risk.

A second possibility is that naproxen, unlike most NSAIDs, affords cardioprotection, just like aspirin. Although there is some evidence for a prolonged pharmacodynamic effect of naproxen,[61] there is a paucity of data on the clinical pharmacology of this compound. Epidemiological studies are divided. For example, Garcia Rodriguez et al.[62] failed to detect a cardioprotective effect of any of the NSAIDs, including naproxen, in the UK GP database. Others utilised the subset of patients within the same database who had rheumatoid arthritis and claimed to detect a reduced likelihood of a myocardial infarction in patients receiving naproxen.[63] Ray et al.[64] reported a failure to detect evidence of a cardioprotective effect of prescribed naproxen in more than 180 000 users and controls in the Tennessee Medicaid database. Kimmel and colleagues,[65] by contrast, performed a telephone survey and found that prescribed and over-the-counter NSAIDs – including naproxen – were associated with a reduced likelihood of myocardial infarction. However, the intrinsic limitations of epidemiological analyses limit the ability to deliver a clear answer on this issue and a prospective controlled trial is unlikely to be performed.

Given that it remains unclear what, if any, cardiovascular effects coxibs have, provision of the primary clinical data from all trials of coxibs to a neutral adjudicator would seem the best opportunity to accumulate sufficient information in high-risk patients to address this issue.

To summarise, multiple factors including aspects of the trial design, patient substrate, adjuvant aspirin, choice of comparator, dose and relative selectivity of the coxib may have contributed to the apparently disparate cardiovascular outcomes in CLASS and VIGOR.

3.3 Renovascular Outcomes

The renal effects of the coxib drugs also deserve attention. Conventional NSAIDs are known to cause sodium and water retention.[66] They have been associated with exacerbations of hypertension in individual patients and may complicate control of blood pressure with antihypertensive drugs. These effects are more noted in the elderly and under renoprival conditions and are thought to be mediated through both COX-1- and COX-2-dependent mechanisms. For example, rofecoxib 12.5mg or 25mg daily and indomethacin 50mg reduced the glomerular filtration rate in salt-depleted elderly patients to similar degrees.[66] Similarly, the limited data published thus far suggests that selective COX-2 inhibitors may induce similar alterations in blood pressure in

similar high-risk patients.[15,66-68] Blood pressure elevation was crudely recorded as an adverse event in phase II and phase III studies of the coxibs. The incidence of an increase in blood pressure positively correlated with both dose and COX-2 selectivity. Given the experience in the mouse,[19] it is possible that the renovascular profiles of coxibs and traditional NSAIDs might diverge, if the degree of COX-2 inhibition and the selectivity with which it is attained are both relevant to these complications.

4. Summary

In summary, the outcome of the VIGOR study affords the most definitive support for the COX-2 paradigm in inflammation, i.e. that selective COX-2 inhibition can achieve anti-inflammatory effects with a reduction in gastrotoxicity compared with traditional NSAIDs. However, the place of coxibs versus conventional NSAIDs continues to be debated.[69] Unresolved issues include the trade-off in benefit versus cost; whether their benefit is most pertinent to those at high risk of GI adverse reactions to NSAIDs and whether adjuvant aspirin should be used and if so whether it would obviate the GI benefit.

The absolute clinical relevance of potential cardiovascular and renal toxicity requires further elucidation. In the interim, selective COX-2 inhibitors are clearly indicated for the treatment of chronic inflammatory conditions in patients with a prior history of GI toxicity with traditional NSAID use. The magnitude of any potential increased cardiovascular risk of selective COX-2 inhibitors in low cardiovascular risk patients is very unlikely to outweigh the benefit of reduced GI toxicity. Furthermore, concomitant therapy with low-dose aspirin is appropriate in patients considered at high risk for cardiovascular events who are prescribed selective COX-2 inhibitors.

As with so much in medicine, the evidence that has been accumulated is incomplete and the art of medicine is still brought to bear in weighing the choices for the individual patient.

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Correspondence and offprints: Dr *Emma A. Meagher*, Department of Medicine and Center for Experimental Therapeutics, University of Pennsylvania School of Medicine, 9055 West Gates Pavilion, 3400 Spruce St, Philadelphia, PA 19104, USA.
E-mail: emma@spirit.gcrc.upenn.edu