

Theme Issue Article

Does a coxib-associated thrombotic risk limit the clinical use of the compounds as analgesic anti-inflammatory drugs?

Arguments in favor

Debabrata Mukherjee

Division of Cardiovascular Medicine, Gill Heart Institute, University of Kentucky, Lexington, Kentucky, USA

Summary

Non-steroidal anti-inflammatory agents (NSAIDs) and selective cyclooxygenase (COX-2) inhibitors (coxibs) are commonly used as analgesic and anti-inflammatory agents. Selective COX-2 inhibitors or coxibs were primarily developed as a response to the gastrointestinal toxicity of conventional NSAIDs but may have other side effects. Currently available data suggests definite prothrombotic risk with the coxibs, and the magnitude of risk may vary with individual agents. Based on available data, coxibs should be restricted to use as 2nd-line, possibly as 3rd-line, agents for carefully chosen patients and randomized trials versus placebo or an accepted comparator must be performed to define the overall safety profile in diverse patient populations. The recently announced Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION)

trial will assess the relative cardiovascular safety of three of the most commonly used pain relievers in the treatment of arthritis patients, ibuprofen, naproxen and celecoxib. The study will enroll patients with osteoarthritis, the most common form of arthritis, who have known coronary heart disease or who have multiple risk factors for heart disease and also some patients with rheumatoid arthritis. Patients will be followed for an average of two years to track the occurrence of serious cardiovascular events, including death, heart attack and stroke. This study should provide some definitive evidence of the relative cardiovascular safety of the available anti-inflammatory agents but would be even more useful if it included an arm where patients were treated with analgesics such as acetaminophen and/or moderate strength narcotics.

Keywords

Acute myocardial infarction, coxib, atherothrombosis, cyclooxygenase-2, prothrombotic

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Introduction

Traditional non-steroidal anti-inflammatory agents (NSAIDs) and the selective cyclooxygenase (COX)-2 inhibitors (coxibs) have been used as analgesic and anti-inflammatory agents in a myriad of patients. Selective COX-2 inhibitors or coxibs were primarily developed as a response to the gastrointestinal toxicity of conventional NSAIDs (1). However, coxibs decrease vascular prostacyclin production and may disrupt the homeostatic mechanisms that limit the effects of platelet activation (2). Several observational and, more recently, randomized trials have raised concerns about the prothrombotic risk of the coxibs. This article reviews the potential prothrombotic risk of coxibs, and outlines the need for dedicated randomized clinical trials with cardiovascular events as the primary endpoint to definitively assess the cardiovascular effects of coxibs.

Coxibs

The development of coxibs as anti-inflammatory agents was based on the knowledge that COX-1 predominates in the stomach, yielding protective prostaglandins, while COX-2 is induced in inflammation giving rise to pain, swelling and discomfort. Thus coxibs would be less likely to cause gastrointestinal toxicity. However, coxibs decrease vascular prostacyclin production and may affect the balance between prothrombotic and anti-thrombotic eicosanoids (3). Unlike the platelet inhibition afforded by COX-1 inhibitors, coxibs do not share this beneficial

Correspondence to:
Debabrata Mukherjee, MD, FACC
Division of Cardiovascular Medicine
Gill Heart Institute
University of Kentucky
900 S. Limestone
Lexington, KY 40536-0200, USA
Tel.: +1 859 323 5630, Fax: +1 859 323 6475
E-mail: Mukherjee@uky.edu

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antithrombotic property. In contrast, by decreasing vasodilatory and anti-aggregatory prostacyclin production, coxibs may tip the balance in favor of pro-thrombotic eicosanoids (thromboxane A₂) and may lead to increased cardiovascular thrombotic events (4).

Available data

Preclinical data

Several basic research studies point to cardioprotective effect of COX-2 and potential detrimental effect of coxibs. Shinmura et al. demonstrated that COX-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning (5). The authors examined the role of COX-2 in the late phase of ischemic preconditioning in a total of 176 conscious rabbits. Ischemic preconditioning (six cycles of 4-min coronary occlusions/4-min reperfusion) resulted in a rapid increase in myocardial COX-2 mRNA levels followed 24 h later by an increase in COX-2 protein expression and in the myocardial content of prostaglandin E₂ and 6-keto-PGF_(1α). Administration of two unrelated coxibs (NS-398 and celecoxib) 24 h after ischemic preconditioning abolished the ischemic-preconditioning-induced increase in tissue levels of PGE₍₂₎ and 6-keto-PGF_(1α). The same doses of NS-398 and celecoxib, given 24 h after ischemic preconditioning, completely blocked the cardioprotective effects of late preconditioning against both myocardial stunning and myocardial infarction, indicating that COX-2 activity is necessary for this phenomenon to occur. These results demonstrate that up-regulation of COX-2 plays an essential role in the cardioprotection afforded by the late phase of ischemic preconditioning. Therefore, this study identified COX-2 as a cardioprotective protein (5). In another study, Hennen et al. demonstrated that the observed increase in time to occlusion with aspirin in a canine coronary thrombosis model was abolished with celecoxib (6). In this study, circumflex coronary artery thrombosis was induced in dogs by electrolytic injury. Oral high-dose aspirin with an endothelial recovery period produced a significant increase in time to vessel occlusion. The observed increase in time to occlusion was abolished when celecoxib was administered to animals dosed with aspirin. The vasomotor effect of endothelium-derived prostacyclin was also examined by monitoring coronary flow during intracoronary administration of arachidonic acid or acetylcholine. In celecoxib-treated animals, vasodilation in response to arachidonic acid was reduced significantly compared with controls. The results of this study indicated important physiological roles for COX-2-derived prostacyclin and raised concerns regarding an increased risk of acute vascular events in patients receiving coxibs (6). Other salutary effects of COX-2 have also been demonstrated in the heart. Dowd et al. demonstrated that inhibition of cyclooxygenase-2 aggravates doxorubicin-mediated cardiac injury *in vivo* suggesting potential beneficial effects of COX-2 in the heart (7). Doxorubicin induces COX-2 activity in rat neonatal cardiomyocytes and this expression of COX-2 limits doxorubicin-induced cardiac cell injury. Doxorubicin increased cardiac injury, detected as a rise in plasma cardiac troponin T, serum lactate dehydrogenase, and cardiomyocyte apoptosis was aggravated by coadministration of SC236 (coxib) but not SC560 (COX-1 inhibitor). These data further support beneficial effects of COX-2 in the heart.

Cheng et al. used a transgenic knockout mice model to further elucidate the important physiological role of COX-2 enzyme in vascular homeostasis (8). The investigators studied deletions of the prostaglandin receptor to understand the effects of coxibs *in vivo*. Mice with absent prostaglandin receptor (IPKO) should mimic the clinical effect of taking coxibs, as these drugs would inhibit prostaglandin production without affecting thromboxane (TXA₂). The COX-2 knockout resulted in enhanced proliferative response to injury and significant increase in TXA₂ biosynthesis (8). These results suggest that PGI₂ may modulate the platelet-vascular interactions *in vivo* and that PGI₂ may have a beneficial effect by specifically limiting the prothrombotic response to TXA₂. These, *in-vivo* gene knockout studies raised further concern about the prothrombotic effects and cardiovascular safety of COX-2 inhibitors.

Egan et al. demonstrated that antagonism or deletion of the receptor (TP) for the cyclooxygenase product thromboxane TXA₂ is more effective than combined inhibition of COX-1 and COX-2 in retarding atherogenesis in Apobec-1/LDLR DKO mice, which may reflect activation of the receptor by multiple ligands during disease initiation and early progression (9). Despite early intervention, selective inhibition of COX-2, alone or in combination with a TP antagonist, failed to modify disease progression but may undermine plaque stability when combined with the antagonist. The study suggests that because TP antagonism may mimic the effect of low-dose aspirin, coincidental treatment with a coxib may undermine the benefit of aspirin by predisposing atherosclerotic plaques to destabilization with subsequent formation of a vasoocclusive thrombosis (9).

Clinical data

The potential clinical cardiovascular toxicity of coxibs was first reported in 2001 by Mukherjee et al. (10). This analysis was based on all available data at that time which included in addition to the Vioxx Gastrointestinal Outcomes research Study (VIGOR) and the Celecoxib Arthritis Safety Study (CLASS), other trials reported to the Food and Drug Administration (FDA) but neither published nor presented. The Vioxx Gastrointestinal Outcomes research Study (VIGOR) trial was a double-blind, randomized, stratified, parallel group study of 8,076 patients to compare the occurrence of gastrointestinal toxicity of rofecoxib 50 mg daily or naproxen 1000 mg daily during chronic treatment for patients with rheumatoid arthritis (11). Aspirin use was not permitted in the study. The baseline characteristics between the treatment groups in the VIGOR trial demonstrated no meaningful or significant differences. Ninety-eight cases (65/4,047 from rofecoxib and 33/4,029 from naproxen) were sent for adjudication of vascular events. Of these 46 patients in the rofecoxib group, and 20 in the naproxen group were adjudicated to have thrombotic cardiovascular serious adverse events. The results of the event-free survival analysis on the 66 cases showed that the relative risk of developing a cardiovascular event in rofecoxib treatment arm was 2.37 (1.39–4.06), *p*=0.0016 (12, 13). A subgroup analysis was performed for “aspirin indicated” and “aspirin not indicated” patients in the VIGOR trial. In this trial, aspirin indicated patients were defined as subjects with past medical history of stroke, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass

graft surgery, or percutaneous coronary interventions. Only 321 (3.9%) patients were aspirin indicated patients (170 in rofecoxib and 151 in naproxen), as need for aspirin was an exclusion criterion. The relative risk ratio of developing serious cardiovascular events in aspirin indicated patients between rofecoxib and naproxen was 4.89 (1.41 – 16.88), $p = 0.012$, and the relative risk for aspirin not indicated patients was 1.89 (1.03 – 3.45), $p = 0.04$ (11–13).

Studies 085 and 090, although not published, were reported to the FDA by the manufacturer of rofecoxib. Study 085 tested the efficacy and safety of rofecoxib versus nabumetone, had a sample size of 1,042 patients and allowed use of low-dose aspirin for prevention of ischemic events (12, 13). There were three total cardiovascular events in this trial with one event with rofecoxib (0.2 %) as compared to 2 (0.4 %) in the nabumetone group and 0 (0 %) in the placebo group. Study 090 with a similar design as study 085, reported a total of six serious cardiovascular events with rofecoxib (1.5%) as compared to 2 (0.5 %) in the nabumetone group and 1 (0.5 %) in the placebo group (12, 13).

An FDA-funded study analyzed the medical records of 1.4 million people insured by the Kaiser Permanente health maintenance organization and treated with a COX-2 selective or non-selective NSAID between January 1, 1999 and December 31, 2001. Patients were entered into the study cohort beginning with their first prescription and followed until the end of the study period, disenrollment, myocardial infarction, or death. During 2,302,029 person-years of follow-up, 8,143 cases of serious coronary heart disease occurred, of which 2,210 (27.1%) were fatal. Multivariate adjusted odds ratios (OR) versus celecoxib were: for rofecoxib (all doses), 1.59 (95% CI 1.10–2.32, $p=0.015$); for rofecoxib 25 mg/day or less, 1.47 (0.99–2.17, $p=0.054$); and for rofecoxib greater than 25 mg/day, 3.58 (1.27–10.11, $p=0.016$). For naproxen versus remote NSAID use the adjusted odds ratio was 1.14 (1.00–1.30, $p=0.05$) (14). The primary finding was that rofecoxib use increased the risk of serious coronary heart disease compared with celecoxib use and that naproxen use does not protect against serious coronary heart disease.

Definitive data regarding the cardiovascular toxicity of rofecoxib was obtained from the Adenomatous Polyp Prevention on VIOXX (APPROVe) trial (15). This was a multi-center, randomized, placebo-controlled, double-blind study to determine the effect of 156 weeks (three years) of treatment with rofecoxib on the recurrence of neoplastic polyps of the large bowel in patients with a history of colorectal adenoma (15). The trial enrolled 2,600 patients and compared rofecoxib 25 mg to placebo. The original article included a post-hoc hypothesis that curves for confirmed thrombotic events would not begin to diverge until after 18 months of exposure to rofecoxib (15). A correction was published on this trial recently which stated that in this randomized, placebo-controlled trial, the authors found an increased risk of confirmed thrombotic events associated with the use of rofecoxib. Visual inspection of the Kaplan–Meier curves suggested that there was an increased frequency of thrombotic events associated with rofecoxib therapy after 18 months (16). However, all intention-to-treat analyses showed that the event curves begin to diverge much earlier, generally within four to six months. The most useful Kaplan-Meier curves, involving intention-to-treat analysis of the widely used end point of the Anti-

platelet Trialists' Collaboration (APTC) study end point, showed divergence after only three months of exposure to rofecoxib (Fig. 1) (17). Based on the APPROVe data, the trial was prematurely terminated and a decision made by the manufacturer to voluntarily withdraw rofecoxib (18).

Celecoxib has not been studied as extensively as rofecoxib with regards to cardiovascular effects. The Celecoxib Arthritis Safety Study (CLASS) was a double-blind, randomized controlled trials of 8,059 patients, in which patients were randomized to receive celecoxib 400 mg twice per day, ibuprofen, 800 mg three times per day, or diclofenac, 75 mg twice per day (19). Aspirin use (<325 mg/day) was permitted in this study. The CLASS trial with celecoxib demonstrated no significant difference in cardiovascular events as compared to the NSAIDs.

The Adenoma Prevention with Celecoxib (APC) trial included 2,026 patients taking either 400-mg or 800-mg daily doses of the drug for an average of 33 months and was primarily designed to assess whether Celebrex can prevent colon polyps. The study was terminated early by the National Institutes of Health (NIH); patients taking 400 mg of Celebrex daily had an approximately 2.5-fold increase in risk of suffering a major cardiovascular event and those taking the 800-mg daily dose had a 3.4-fold increased risk compared with subjects taking placebo (20) (Fig. 2). Overall, there were a total of six cardiovascular-related events in the placebo group, compared with 15 in the 400-mg group and 20 in the 800-mg group.

There are even fewer studies assessing the cardiovascular safety of the newer coxibs. The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), the largest coxib

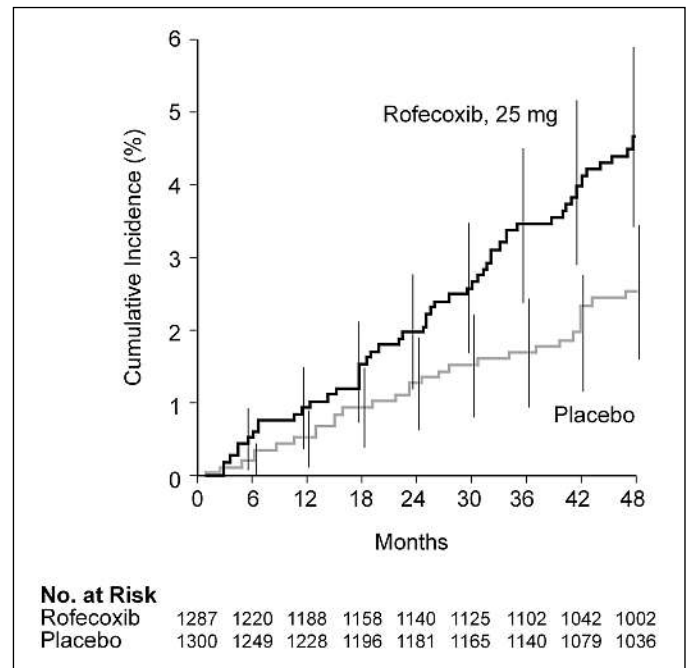


Figure 1: Kaplan–Meier estimates of the cumulative incidence of confirmed APTC events in the rofecoxib and placebo groups, according to the intention-to-treat principle. Vertical lines indicate 95% confidence intervals. Adapted from (17).

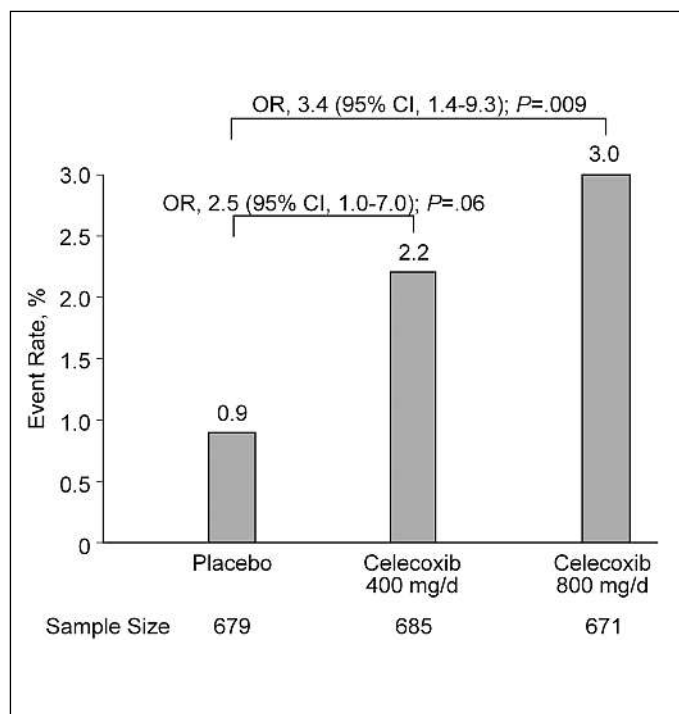


Figure 2: Event rates of cardiovascular death, myocardial infarction, and stroke in the Adenoma Prevention With Celecoxib (APC) Trial. The difference for events between the 400-mg and 800-mg dose was not significant (OR, 0.7 [95% CI, 0.4–1.4]; $P=0.30$). OR, odds ratio; CI, confidence interval. The dose response trend across all groups, $P=0.007$. Adapted from (18).

trial to date, enrolling 18,325 patients with osteoarthritis again raised the concern of an excess of myocardial infarctions with lumiracoxib compared with naproxen (18 [0.38%] vs. 10 [0.21%]; hazard ratio 1.77 [95% CI 0.82–3.84]), although most of these events were non-fatal and the elevated risk was not statistically significant (21). However, the trial was not adequately powered to assess differences in cardiovascular outcomes. In patients who were not taking low-dose aspirin, the hazard ratio climbed even higher.

A meta-analysis of trials with valdecoxib, another selective COX-2 inhibitor suggested that this agent was also associated with increased risk of major cardiovascular events. The meta-analysis included two placebo-controlled trials of valdecoxib used as pain control in CABG patients along with several other placebo-controlled studies of the drug in arthritis patients (22, 23). Valdecoxib in the combined analysis was associated with a three-fold higher risk of cardiovascular events than placebo (relative risk 3.08; 95% CI 1.20 – 7.87) (24, 25). The CABG trials tested a combination of valdecoxib and its prodrug (parecoxib), the prodrug being given initially for fast onset of action, followed by valdecoxib orally.

An Adverse Event Reporting System (AERS) search by FDA revealed 144 unduplicated thrombotic or embolic cases for celecoxib and 159 cases for rofecoxib. Forty-two celecoxib cases and 60 rofecoxib cases were excluded for either lack of documented event, hemorrhagic strokes in which PT, PTT or INR was above the normal range, or second hand reports with no confirmed diagnosis. Ninety-nine thrombotic or embolic events were attributed to rofecoxib and 102 cases to celecoxib (26).

Table 1: Trials with selective COX-2 inhibitors and cardiovascular outcomes.

Agent	Trial	Design	Results
Rofecoxib	VIGOR	Rofecoxib 50 mg qd vs. naproxen 500 mg bid in patients with arthritis	Relative risk of developing a cardiovascular event in rofecoxib arm was 2.37 (95% CI 1.39 – 4.06), $p=0.0016$.
Rofecoxib	APPROVe	Rofecoxib 25 mg qd for preventing recurrence of colorectal polyps	At 18-months, rate of MI/stroke for rofe-coxib vs. placebo was 3.6% vs. 2.0% ($P < 0.001$).
Celecoxib	CLASS	Celecoxib 400 mg bid vs. Diclofenac 75 mg bid vs. Ibuprofen 800 mg tid in patients with arthritis	Rate of MI with celecoxib: 1.6% and with diclofenac/ibuprofen: 1.2% $P = NS$.
Celecoxib	APC	Celecoxib 400 or 800 mg qd in preventing colon polyps	Compared with placebo, 400 mg of celecoxib daily increased risk of cardiac events by 2.5-fold and 800 mg increased risk 3.4-fold.
Celecoxib	PreSAP	Celecoxib 400 mg qd in colorectal cancer	Preliminary reports from manufacturer suggest celecoxib was not associated with increased cardiovascular risk.
Celecoxib	ADAPT	Celecoxib 400 mg qd vs. naproxen 200 mg bid vs. placebo for Alzheimer's disease prevention	No increase in cardiovascular events with celecoxib but naproxen increased the risk of MI/stroke by 50% in preliminary report.
Lumiracoxib	TARGET	Lumiracoxib 400 mg qd vs. naproxen 500 mg bid vs. Ibuprofen 800 mg tid in arthritis	Nonsignificant excess of myocardial infarctions with lumiracoxib compared with naproxen with hazard ratio 1.77 [95% CI 0.82–3.84]).
Valdecoxib	Meta-analysis	Valdecoxib (10–80 mg daily), nonselective NSAID and placebo data from 7500 osteoarthritis and rheumatoid arthritis patients	Valdecoxib was associated with more than twice as many myocardial infarctions or stroke events than placebo [relative risk 3.08; 95% CI 1.20 – 7.87].

ADAPT = Alzheimer's Disease Anti-inflammatory Prevention Trial, APC = Adenoma Prevention with Celecoxib, APPROVe = Adenomatous Polyp Prevention on Vioxx, CLASS = Celecoxib Long-term Arthritis Safety Study, PreSAP = Prevention of Spontaneous Adenomatous Polyps, TARGET = Therapeutic Arthritis Research and Gastrointestinal Event Trial, VIGOR = Vioxx Gastrointestinal Outcomes Research, MI = Myocardial infarction, CI = Confidence interval.

Figure 3: Spectrum of biological activity of currently available non steroidal anti-inflammatory drugs. Each agent has potentially different effect on thromboxane and prostacyclin synthesis (GI = gastrointestinal). Adapted from (2).

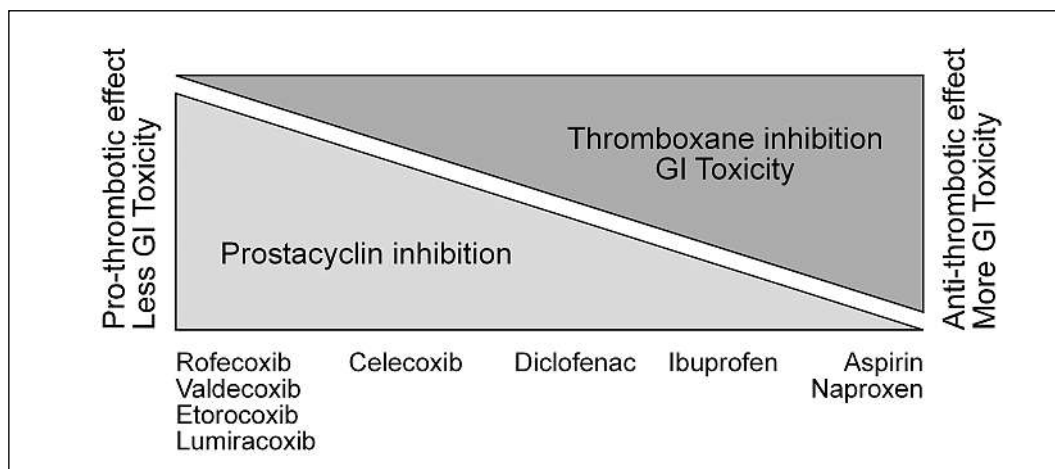


Table 1 lists available data from trials with coxibs which reported cardiovascular event data. Cardiovascular outcomes were not the primary outcomes in any one of these trials and the patient populations in these trials were relatively healthy, without multiple cardiac risk factors. The low cardiovascular risk of the population studied and the short follow-up in the trials to date may significantly underestimate the magnitude of the hazard. Also, the trials examined only addressed continuous use of coxibs. Currently, no data exists on cardiovascular safety for the sporadic, intermittent use of these agents by individuals for musculoskeletal pain, which appears to be the most frequent pattern of use. There are also major differences in the patient population studied in the different trials. It is clinically useful to consider non-selective and selective COX inhibitors as possessing a spectrum of biological effects, favorable and unfavorable (Fig. 3). On one end of the spectrum, coxibs show less propensity for gastrointestinal toxicity, but greater prothrombotic potential. At the other end of the spectrum, COX-1 inhibitor such as aspirin show greater potential for gastrointestinal toxicity, but have a cardio-protective effect. Other agents fall along intermediate points in this spectrum. Clinicians may want to consider these patterns of risk and benefit in selecting the most appropriate agent for individual patients based on individual gastrointestinal and cardiovascular risk profile.

Conclusions

NSAIDs and coxibs continue to be used for a myriad of disease conditions for relief of pain and inflammation. Currently available data suggests definite prothrombotic risk with the coxibs and the magnitude of risk may vary with individual agents. The coxibs have been marketed intensively by direct-to-consumer advertising in the USA, and sales of these drugs exceed US\$7 billion per year. However, it is hard to justify this extraordinary adoption of coxibs in light of marginal efficacy, heightened risk, and excessive cost compared with traditional NSAIDs. The coxib debate will not go away until safety and efficacy questions are definitively answered.

The FDA Advisory Panel on coxibs recently concluded that i) coxibs increase the risk for cardiovascular events; ii) the risk ap-

pears to differ across individual drugs within the coxib class; and iii) the cardiovascular risk may be dose related, possibly duration related; and there is no evidence that aspirin prevents or attenuates the observed risk. As a result, iv) coxibs should be restricted to use as second-line, possibly as third-line, agents for carefully chosen patients; and v) randomized trials versus placebo or an accepted comparator must be performed, to better define the overall safety profile in diverse patient populations (27).

Future directions and trials

A major reason for the mass confusion surrounding cardiovascular effects of selective coxibs is the lack of a dedicated trial to assess cardiovascular safety. Without such a trial, one cannot meaningfully interpret interdrug differences, because the patient populations in the various trials were different; the drug doses, strength, and duration of therapy were different; and each of the drugs in the coxib class are distinct molecules with specific biological properties. Furthermore, nearly half of the patients with arthritis have coexisting cardiovascular disease, and essentially no trials have addressed this important group of patients and there exists a vacuum of knowledge. Coxibs may still have an important therapeutic role, but we need dedicated, prospective randomized trials to assess their cardiovascular safety before resuming their use. An ideal trial would prospectively compare several of the coxib agents with naproxen and placebo in patients without established cardiovascular disease in a double-blind randomized manner. However, such a trial would need to recruit several thousands of patients in each arm to have enough power to detect a significant difference in cardiovascular risk between the agents. The total sample size of such a study may well exceed 40,000 patients and may not be feasible to do. On the other hand, a trial which evaluates coxibs in patients *with* established vascular disease would need less than half the sample size of ~ 15,000 – 20,000 patients and may be logistically more feasible and, although the ethical implications of such a trial may be debated, would at least provide some definitive answers regarding safety of coxibs in patients with known vascular disease.

The recently announced Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen

(PRECISION) trial will assess the relative cardiovascular safety of three of the most commonly used pain relievers in the treatment of arthritis patients, ibuprofen, naproxen and celecoxib. The study will primarily enroll patients with osteoarthritis, the most common form of arthritis, who have known coronary heart disease or who have multiple risk factors for heart disease and also some patients with rheumatoid arthritis. Patients will be followed for an average of two years to track the occurrence of serious cardiovascular events including death, heart attack and stroke. The PRECISION trial will compare celecoxib, the least selective coxib with ibuprofen, which has a similar selectivity, and with the non-selective naproxen. The trial is therefore less

likely to be associated with increased cardiovascular risks for the patients compared to more selective coxibs. Furthermore, low-dose aspirin will be permitted in the study which might have an interaction with the ibuprofen arm. Some prior studies have suggested that treatment with ibuprofen blocks the inhibition of platelet COX-1 activity and the impairment of platelet aggregation by aspirin (28, 29) but other reports have disputed these findings (30). Nevertheless, this study should provide some definitive evidence of the relative cardiovascular safety of the available anti-inflammatory agents and would have been even more useful if it included an arm where patients were treated with analgesics such as acetaminophen and/or moderate strength narcotics.

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