Coxibs and Heart Disease: What We Have Learned and What Else We Need to Know

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STATE-OF-THE-ART PAPER

Coxibs and Heart Disease

What We Have Learned and What Else We Need to Know

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Since their approval in 1998, the popularity of selective cyclooxygenase-2 (COX2) inhibitors has swung from a domination of drug sales to serious disputes about their cardiovascular safety. Despite the numerous studies on COX2 inhibitors that have emerged, drawing conclusions about their cardiovascular safety has been complicated by conflicting results, underpowered clinical trials, and the lack of a placebo group and use of post hoc analyses in many trials. Nonetheless, certain conclusions can be made with reasonable accuracy. This review addresses the controversy in 3 segments. It begins with a discussion of the several mechanisms proposed to explain how selective COX2 inhibition impacts the cardiovascular system. This is followed by a recount of the several clinical studies that delved into the cardiovascular outcomes associated with COX2 inhibitors. Finally, answers to key questions are provided to assist the clinician in devising a systematic approach to the risk-benefit analysis of COX2 inhibitors in actual practice. (J Am Coll Cardiol 2007;49:1–14) © 2007 by the American College of Cardiology Foundation

The transformation of arachidonic acid to prostaglandin H2 (PGH2) is a step that commits arachidonic acid down the path of prostaglandin-thromboxane synthesis. This transformation is catalyzed by cytosolic prostaglandin G/H synthase, more commonly known as cyclooxygenase (COX). Prostaglandin H2 is an unstable intermediate and is further converted to one of many prostanoids, such as prostacyclin (PGI2) and thromboxane A2 (TXA2), by tissue-specific isomerases. As early as 1987, evidence emerged showing that the COX enzyme probably existed in 2 isoforms (1). Today it is well established that these isoforms, COX1 and COX2, exist and are encoded by separate genes on different chromosomes.

Cyclooxygenase inhibition formed the basis for the success of non-steroidal anti-inflammatory drugs (NSAIDs) in treating a variety of pain syndromes. The drawback, however, was that every year, 2% to 4% of patients taking NSAIDs suffered from symptomatic gastrointestinal ulcers and their complications (2). As the science behind the COX enzyme progressed, it became apparent that COX2 inhibition mediated the anti-inflammatory effects of NSAIDs, whereas COX1 inhibition was responsible for the adverse effects on the gastrointestinal tract. It therefore became reasonable to assume that inhibiting COX2 selectively would result in the same anti-inflammatory benefits that nonselective NSAIDs provided but with fewer gastrointestinal side effects. This rekindled the interest of pharmaceutical industries in manufacturing new analgesic and anti-inflammatory medications known as selective COX2 inhibitors or coxibs. In 1995, the first generation of coxibs, celecoxib (by Monsanto) and rofecoxib (by Merck), entered clinical trials. In 1998, celecoxib was approved by the U.S. Food and Drug Administration (FDA), followed by rofecoxib in 1999. These drugs soon dominated the prescription-drug market for NSAIDs. By October 2000, celecoxib and rofecoxib had sales exceeding $3 billion in the U.S. (3).

At the time that COX2 inhibitors were approved, randomized trials aimed at proving their gastrointestinal safety were still ongoing. It was not until 2000 that 2 large studies, CLASS (Celecoxib Long-Term Arthritis Safety Study) (2) and VIGOR (Vioxx Gastrointestinal Outcomes Research) (4), showed their superior gastrointestinal profile over conventional NSAIDs. Both studies, however, were not free of controversy. For the CLASS trial, the gastrointestinal superiority of celecoxib in its 6-month data became disputable when this superiority failed to manifest in its 12-month data (5). On the other hand, the VIGOR study raised concerns about the cardiovascular safety of rofecoxib. To amplify this concern, near the time of completion of the VIGOR study, preliminary evidence supporting the biologic plausibility of COX2-induced adverse cardiovascular events emerged. From hereon, the use of coxibs became plagued by safety concerns on the basis of both mechanistic and clinical data.

As a result of the evolving understanding of the potential risks of selective COX2 inhibition, in 1999, Merck introduced a standard operating procedure to evaluate and

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CAD = coronary artery disease
CHF = congestive heart failure
COX = cyclooxygenase
FDA = Food and Drug Administration
HR = hazard ratio
MI = myocardial infarction
NSAID = non-steroidal anti-inflammatory drug
OA = osteoarthritis
PG = prostaglandin
PPI = proton pump inhibitor
RA = rheumatoid arthritis
TX = thromboxane

adjudicate cardiovascular events in all ongoing and future rofecoxib clinical trials (6). In 2002, the FDA also issued a new warning in the package insert of rofecoxib, stating that ". . . caution should be exercised when Vioxx is used in patients with a medical history of ischemic heart disease." This decision of the FDA to opt for a mere label change and not a more practice-changing intervention, such as compelling manufacturers to initiate trials on cardiovascular safety, has been highly criticized (7). As a matter of fact, for a good number of years after the VIGOR trial stirred controversy, no randomized controlled trial was initiated to address the cardiovascular toxicity of coxibs as a primary end point. Instead, more trials were designed to show the efficacy of coxibs for other indications, such as the prevention of recurrent colonic polyps, management of postoperative pain, and slowing down of the progression of Alzheimer's dementia. One such trial was the APPROVe (Adenomatous Polyp Prevention on Vioxx) study (8), which now stands among landmark clinical trials. It was prematurely terminated after investigators found an increased cardiovascular risk among patients taking rofecoxib, and served as the basis for the immediate worldwide withdrawal of rofecoxib by Merck on September 30, 2004. Thousands of lawsuits against Merck followed this event, because by this time an estimated 80 million people had already taken the drug (9).

Not too long thereafter, the results of 2 more randomized trials of coxibs were published and showed unfavorable cardiovascular outcomes as well. One was a celecoxib trial for colonic adenoma prevention (10), and the other was a valdecoxib/parecoxib trial for the management of postoperative pain after coronary artery bypass grafting (CABG) (11). In addition to being linked with a heightened cardiovascular risk, valdecoxib and parecoxib had previously been implicated in life-threatening hypersensitivity reactions, including anaphylaxis, angioedema, Stevens-Johnson syndrome, and toxic epidermal necrolysis (12). Consequently, on April 7, 2005, the FDA requested that Pfizer remove valdecoxib from the market. Furthermore, the FDA issued a cautionary note against the coxibs, and NSAIDs in general: ". . . an increased risk of serious adverse [cardiovascular] events appears to be a class effect of NSAIDs (excluding aspirin). The FDA has requested that the package insert for all NSAIDs, including Celebrex, be revised to include a boxed warning to highlight the potential increased risk of [cardiovascular] events and . . . to include a contraindication for use in patients immediately postoperative from CABG" (13).

In the following discussion, we highlight the several mechanisms that have emerged to explain how selective COX2 inhibition impacts the cardiovascular system. We then review the landmark clinical studies that delved into the cardiovascular outcomes associated with coxibs. Finally, we present a systematic approach to the risk-benefit analysis of coxibs in actual clinical practice.

Mechanisms Underlying the Cardiovascular Effects of Selective COX2 Inhibitors

Cyclooxygenase-1 is expressed constitutively in most cell types and is the only functioning COX in mature platelets. Cyclooxygenase-2, on the other hand, is an isoform with an expression that is induced by inflammatory stimuli such as bacterial endotoxin and cytokines. Induction of COX2 expression has also been demonstrated in atheromatous plaques (14,15) and neoplasms (16). This led to the hypothesis that COX2 inhibition might be useful in the treatment or prevention of atherosclerosis and various cancers. In fact, a few reports have suggested that COX2 inhibition might be cardioprotective. For example, Dinchuk et al. (17) have shown that COX2-knockout mice developed cardiac fibrosis. Two histologic studies, performed by Baker et al. (14) and Schonbeck et al. (15), showed the presence of COX2 in atherosclerotic lesions of native and transplanted coronary arteries, but not in normal coronary arteries. Furthermore, COX2 expression was localized to macrophages/foam cells, medial smooth muscle cells, and endothelial cells within the atherosclerotic plaque, all of which are established key players in atherogenesis. A similar study by Cipollone et al. (18) on carotid plaques showed a significantly higher concentration of COX2 in plaques associated with a recent transient ischemic attack or stroke compared with asymptomatic plaques. Cyclooxygenase 2 expression also appears to be induced by many of the same stimuli implicated in the development of atherosclerosis, including free radicals (19), tumor necrosis factor, interleukin-1 (20), platelet-derived growth factor (21), and increased arterial wall shear stress (22). Finally, because inflammation of the endothelium is known to diminish its capacity to produce nitric oxide, it has been suggested that COX2 inhibition can improve endothelial function in this setting. This was shown by 2 small, short-term studies (≤2 weeks in duration) in which celecoxib led to significant improvements in flow-mediated vasodilation compared with placebo in patients with hypertension or coronary artery disease (CAD) (23,24).

In reality, predicting the effect of COX2 inhibition on the cardiovascular system has not been straightforward. Although COX2 can be viewed as a "bad" player in the atherosclerotic process based on most of the aforementioned data, it can also be regarded as a "good" player if its up-regulation is thought of as a compensatory mechanism

to help maintain vascular health. In addition, in 1998, it became apparent that the 2 COX isoforms affected the balance of vasoactive prostanoids differently. Several studies suggested that TXA2, a vasoconstrictor and promoter of platelet aggregation, was largely COX1-derived, whereas the synthesis of the vasodilator and potent inhibitor of platelet aggregation, PGI2, was linked to COX2 induction (25,26). Specifically, the up-regulation of COX2 (e.g., by interleukin-1β) shifted arachidonic acid metabolism from TXA2 synthesis to the preferential production of PGI2 (27). Furthermore, although nonselective COX inhibitors, such as aspirin and ibuprofen, suppressed TXA2 production in platelets, selective COX2 inhibitors did not (25,26). Altogether, a clear suggestion was made that COX2 inhibition could tip the vascular homeostasis into a prothrombotic state.

More investigations have since led to the unraveling of other mechanisms behind coxib-induced cardiovascular harm. For example, it has been suggested in animal models that COX2 mediates the cardioprotective effects of the late phase of ischemic preconditioning and that PGE2 and PGI2 are the likely effectors of such protection (28,29). Accordingly, COX2 inhibition can block the protective effect of late-phase preconditioning against myocardial stunning and infarction. In another study of mice models of atherosclerosis, antagonism of the TXA2 receptor was shown to retard atherogenesis, but the combination of selective COX2 inhibition and TXA2-receptor antagonism resulted in atherosclerotic lesions that lacked fibrotic caps, suggesting a destabilizing effect on these plaques (30). Wu et al. (31) also showed that when angiogenesis was induced by vascular endothelial growth factor, cell proliferation and the formation of vascular structures were increased in human umbilical vein endothelial cells that overexpressed COX2, whereas cell proliferation was significantly reduced when the endothelial cells were pretreated with a selective COX2 inhibitor. These findings suggest that COX2 may be cardioprotective, in part because of its role in angiogenesis. As will be discussed in later sections of this review, some COX2 inhibitors have been associated with hypertension and oxidative modification of lipids, providing yet another mechanism by which these drugs might produce adverse outcomes.

Risk of Ischemic Cardiovascular Events With Rofecoxib

The first major postmarketing multicenter trials on COX2 inhibitors were the CLASS and VIGOR trials (Tables 1 and 2) (2,4). Although safety concerns were raised by the VIGOR trial, neither of these trials convinced the entire medical community of the increased cardiovascular risk of coxib use. The CLASS trial was a double-blind trial of 7,968 patients with osteoarthritis (OA) or rheumatoid arthritis (RA) who were randomized to high-dose celecoxib, ibuprofen, or diclofenac. Patients were allowed to take cardioprotective doses of aspirin. At the end of 6 months, there was no difference in the incidence of cardiovascular events between the celecoxib and nonselective NSAID groups, irrespective of aspirin use. The VIGOR study was a similar trial that randomized 8,076 patients with RA to either 50 mg rofecoxib daily or 500 mg naproxen twice daily. As in the CLASS trial, the coxib dose was over the maximum recommended dose for long-term administration, and was in keeping with the objective of the study, which was to rigorously assess the gastrointestinal safety of the drug even at supratherapeutic doses. Unlike the CLASS trial, patients in the VIGOR trial were prohibited from using aspirin. During a median follow-up of 9 months, the incidence of myocardial infarction (MI) was several-fold higher in the rofecoxib group: 4-fold higher as reported by the VIGOR study group; 5-fold higher as reported in the FDA files (32). Because the study lacked a placebo arm, it was unclear how much of the increased risk of MI was attributable to a harmful effect of high-dose rofecoxib, a protective effect of naproxen, chance (because of the small number of events), or a combination of these factors.

When this unexpected outcome from rofecoxib unfolded and mechanisms to explain its biologic plausibility emerged, several observational studies were published to help confirm the finding, but the results were conflicting (33–35). Pooled analyses of previous randomized trials likewise did not provide a clear answer to the issue. Three pooled analyses of trials before and after the marketing of rofecoxib, published from 2001 to 2003, supported the cardiovascular safety of rofecoxib (Table 1). These included the studies by Konstam et al. (6) and Reicin et al. (36), which found similar rates of thrombotic events and similar rates of the APTC (Anti-Platelet Trialists' Collaboration) end point (combined incidence of death from cardiovascular, hemorrhagic, or unknown cause; nonfatal MI; and nonfatal stroke) with rofecoxib, placebo, and comparator non-naproxen NSAIDs. The data evaluated by Konstam et al. (6) included the results of the VIGOR trial and indicated that naproxen was an outlier NSAID in that it was associated with a lower risk of cardiovascular events compared with rofecoxib. In an updated review, Weir et al. (37) reiterated in 2003 that rofecoxib was safe from a cardiovascular standpoint. In addition to the pooled analyses of Konstam et al. (6) and Reicin et al. (36), they included data from the Alzheimer's Disease and Mild Cognitive Impairment program, a composite of placebo-controlled trials that again showed similar rates of cardiovascular events in the rofecoxib and placebo groups.

In contrast to the above data, in 2001, Mukherjee et al. (38) published a review highlighting the cardiovascular risk associated with coxibs. In their analysis of the VIGOR study, the relative risk of an adjudicated cardiovascular thrombotic event with rofecoxib compared with naproxen was 2.38 (95% confidence interval [CI] 1.39 to 4.00). They then looked into the rate of similar events in a placebo group, which they derived from a meta-analysis of 4 aspirin

Table 1 Cardiovascular Safety Data for Rofecoxib From Randomized Controlled Trials

Trial	Number of Patients	Patient Characteristics	Intervention	Duration	Cardiovascular Outcome	Results
VIGOR (4)	8,076	RA	Rofecoxib 50 mg/day vs. naproxen 500 mg 2x/day (ASA prohibited)	9 months	MI	↓ Risk with naproxen: RR 0.2 (0.1–0.7)
Pooled analysis of 8 phase IIB/III trials by Reicin et al. (36)	5,435	OA	Rofecoxib 12.5 to 50 mg/day vs. placebo or nonselective NSAIDs (ibuprofen 800 mg 3x/day, diclofenac 50 mg 3x/day, or nabumetone 1,500 mg/day)	Ranged from 6 weeks to 22 months	Arterial and venous thrombotic events	No difference in risks when rofecoxib was compared with all controls In trials that compared rofecoxib with placebo: RR with rofecoxib 0.94 (0.31–2.92) In trials that compared rofecoxib with nonselective NSAIDs: RR with rofecoxib 1.15 (0.63–2.09)
					APTC end point	No difference in risks when rofecoxib was compared with all controls In trials that compared rofecoxib with nonselective NSAIDs: RR with rofecoxib 1.44 (0.65–3.17)
Pooled analysis of 23 phase IIB through V trials by Konstam et al. (6)	28,465	RA, OA, chronic low back pain, or eligibility for prevention or treatment of Alzheimer's dementia	Rofecoxib 12.5 to 50 mg/day vs. placebo, nonselective non-naproxen NSAIDs (ibuprofen, diclofenac, or nabumetone), or naproxen	Ranged from 4 weeks to 2 yrs	APTC end point	No difference when rofecoxib was compared with placebo: RR 0.84 (0.51–1.38) No difference when rofecoxib was compared with non-naproxen NSAIDs: RR 0.79 (0.40–1.55) ↑ Risk with rofecoxib when compared with naproxen: RR 1.69 (1.07–2.69)

Continued on next page

Table 1 Continued

Trial	Number of Patients	Patient Characteristics	Intervention	Duration	Cardiovascular Outcome	Results
Alzheimer's disease and MCI program (67)	2,907	Alzheimer's dementia or mild cognitive impairment	Rofecoxib 25 mg/day vs. placebo	1.2 yrs	APTC end point	No difference between the 2 groups: RR 0.82 (0.51–1.32)
Meta-analysis of 18 RCTs by Jüni et al. (40)	21,432	RA, OA, chronic low back pain	Rofecoxib 12.5 to 50 mg/day vs. placebo or nonselective NSAIDs (ibuprofen 2,400 mg/day, diclofenac 150 mg/day, nabumetone 1,000 to 1,500 mg/day, or naproxen 1,000 mg/day)	Ranged from 4 weeks to 56 weeks	MI	↑ Risk with rofecoxib when compared with all controls: RR 2.24 (1.24–4.02) In trials that compared rofecoxib with placebo: RR with rofecoxib 1.04 (0.34–3.12) In trials that compared rofecoxib with non-naproxen NSAIDs: RR with rofecoxib 1.55 (0.55–4.36) In trials that compared rofecoxib with naproxen: RR with rofecoxib 2.93 (1.36–6.33)
APPROVe (8)	2,586	History of colorectal adenoma; 28% with high cardiovascular risk profile	Rofecoxib 25 mg/day vs. placebo (ASA allowed)	2.5 yrs	Composite of MI, unstable angina, sudden death from cardiac causes, ischemic stroke, TIA, peripheral arterial/venous thrombosis, and pulmonary embolism	↑ Risk with rofecoxib: RR 1.92 (1.19–3.11) Difference in risks mainly due to ↑ number of MIs and strokes in rofecoxib group
					APTC end point	↑ Risk with rofecoxib: RR 2.06 (1.16–3.64)
					Heart failure/pulmonary edema	↑ Risk with rofecoxib: HR 4.61 (1.50–18.83)
					HTN	↑ Risk with rofecoxib: HR 2.02 (1.71–2.38)
					Peripheral edema	↑ Risk with rofecoxib: HR 1.57 (1.17–2.10)

↑ = increased; APTC = Anti-Platelet Trialists' Collaboration; ASA = aspirin; HR = hazard ratio (numbers in parentheses represent the 95% confidence interval); HTN = hypertension; MCI = mild cognitive impairment; MI = myocardial infarction; NSAID = non-steroidal anti-inflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis; RCTs = randomized controlled trials; RR = relative risk (numbers in parentheses represent the 95% confidence interval); TIA = transient ischemic attack.

Table 2 Cardiovascular Safety Data for Celecoxib From Randomized Controlled Trials

Trial	Number of Patients	Patient Characteristics	Intervention	Duration	CV Outcome	Results
CLASS (2)	7,968	OA, RA	Celecoxib 400 mg 2x/day vs. nonselective NSAIDs (ibuprofen 800 mg 3x/day or diclofenac 75 mg 2x/day) (ASA allowed)	6 months (Only 57% of subjects completed 6 months of treatment)	MI	No difference between the 2 groups
					Angina	No difference between the 2 groups
					CVA	No difference between the 2 groups
					HTN	↓ Incidence with celecoxib
					Peripheral edema	No difference between the 2 groups
APC (10)	2,035	History of colorectal adenoma	Celecoxib 200 to 400 mg 2x/day vs. placebo	2.8 to 3.1 yrs	Composite of CV death and nonfatal MI	Dose-related ↑ risk with celecoxib For celecoxib 200 mg 2x/day: HR 3.0 (1.0–9.3) For celecoxib 400 mg 2x/day: HR 3.8 (1.3–11.5)
					Composite of CV death, nonfatal MI, stroke, and heart failure	Dose-related ↑ risk with celecoxib For celecoxib 200 mg 2x/day: HR 2.3 (0.9–5.5) For celecoxib 400 mg 2x/day: HR 3.4 (1.4–7.8)
PreSAP (49)	1,561	History of colorectal adenoma	Celecoxib 400 mg/day vs. placebo	2.7 yrs (suspended thereafter because of APC results)	APTC end point	No difference between celecoxib and placebo: RR with celecoxib 1.0 (0.5–2.1)
ADAPT (49)	2,463	Elderly patients (≥70 yrs) at risk for Alzheimer's dementia	Celecoxib 200 mg 2x/day vs. naproxen 220 mg 2x/day vs. placebo	20 months (suspended thereafter because of APC results)	CV and cerebrovascular events	No difference between celecoxib and placebo ↑ Incidence in naproxen arm compared with placebo arm

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Table 2 Continued

Trial	Number of Patients	Patient Characteristics	Intervention	Duration	CV Outcome	Results
Alzheimer's Disease Study IQ5-97-02-001 (49)	425	Alzheimer's dementia	Celecoxib 200 mg 2x/day vs. placebo	1 yr	CV thrombotic events (composite of MI, stroke, and peripheral vascular thrombosis) MI	Incidence: 2.1% with placebo 3.8% with celecoxib Incidence: 0% with placebo 1.4% with celecoxib
SUCCESS-1 (49)	13,194	OA, RA	Celecoxib 100 or 200 mg 2x/day vs. naproxen 500 mg 2x/day vs. diclofenac 50 mg 2x/day	12 weeks	Composite of MI, ischemic CVA, and peripheral vascular thrombosis MI	No difference among the three groups: incidence 0.3% in each group Incidence: <0.1% with nonselective NSAIDs, 0.1% with celecoxib 200 mg 2x/ day, and 0.2% with celecoxib 100 mg 2x/day

↓ = decreased; CV = cardiovascular; CVA = cerebrovascular accident; other abbreviations as in Table 1.

primary prevention trials. Compared with this placebo group's annualized MI rate of 0.52%, the corresponding rates were higher in the rofecoxib group of the VIGOR trial (0.74%, p = 0.004) and the celecoxib group of the CLASS trial (0.80%, p = 0.02). This analysis, however, was criticized for comparing patients without rheumatoid arthritis (placebo group) with the patients of the VIGOR trial, all of whom had RA and were potentially at an increased risk for cardiovascular events (39).

After rofecoxib was withdrawn from the market based on the results of the APPROVe study, Jüni et al. (40) came out with a meta-analysis of 18 randomized controlled trials that compared rofecoxib with nonselective NSAIDs or placebo in patients with chronic musculoskeletal disorders (Table 1). After analyzing a total of 64 MI events in 21,432 patients, the relative risk of MI with rofecoxib vs. control was 2.24 (95% CI 1.24 to 4.02). Using cumulative meta-analysis, the investigators showed that this significantly increased risk should have become evident as early as 2000. Although estimates of the relative risk varied depending on whether rofecoxib was compared with placebo, a non-naproxen NSAID, or naproxen in the various trials, a test of interaction was not significant and it was concluded that the type of control had no important impact on the relative risk. Interestingly, the investigators showed that the only source of variation in risk of MI related to whether or not adverse events were examined by an external end point committee. In this light, they warned that data on adverse events from industry-sponsored randomized trials were trustworthy only if an independent end point committee was involved (41). To address the question of cardioprotection from naproxen, the investigators analyzed 11 observational studies that compared the cardiovascular risk of naproxen use with that of no NSAID use or use of a non-naproxen NSAID. The combined estimate of the relative risk of MI with naproxen use was 0.86 (95% CI 0.75 to 0.99). It therefore seemed that naproxen had only a small, if any, cardioprotective effect, and this effect alone could not have accounted for the higher MI rates in the rofecoxib arm of trials such as the VIGOR trial.

The verdict on the rofecoxib controversy was finally laid down by Merck when the results of the APPROVe trial came out (Table 1) (8). This trial was designed to test the hypothesis that 3 years of rofecoxib treatment will reduce the risk of recurrent adenomatous polyps in patients with a history of colorectal adenomas. At least 1,000 patients were randomized to 1 of 2 arms, 25 mg rofecoxib daily or placebo, and approximately 28% of the patients were designated as having a high cardiovascular risk profile. Patients were allowed to take low-dose aspirin for cardiovascular protection, although only about 20% actually took aspirin at some point in the study. On September 30, 2004, about 2 months before its planned completion date, the study was terminated after an interim review of the external safety monitoring board found a higher risk of thrombotic events, mainly MI and stroke, in the rofecoxib arm. Among those who took rofecoxib, this risk was especially high in those

who had a history of symptomatic atherosclerotic cardiovascular disease or diabetes. Although the original article suggested that the excess risk surfaced only after 18 months of rofecoxib use, a correction to this claim was recently made; a re-analysis of the data did not suggest that a shorter course (<18 months) of rofecoxib was safe (42). Although the APPROVe trial was a relatively small trial that was not designed primarily to investigate cardiovascular outcomes, it brought forward a new dimension to the rofecoxib analysis by using placebo as the control and having a treatment and follow-up duration well beyond 24 months. Thereafter Merck could have accepted a black box warning, but it chose to pull the drug out of the world market immediately.

On May 11, 2006, Merck released their data on an off-drug extension of the APPROVe trial in which they followed up the over 2,500 patients for another year after discontinuation of the study drug (43). There continued to be more cardiovascular thrombotic events in those previously randomized to rofecoxib (28 events vs. 16 events in those previously randomized to placebo), with a relative risk of 1.64 (95% CI 0.89 to 3.04). When the off-drug extension data were combined with the 3-year on-drug data, the relative risk over 4 years was 1.74 (95% CI 1.19 to 2.55), hinting that the increased cardiovascular risk in those who took rofecoxib was slow to abate—in fact, more slowly than expected if the only mechanism invoked was a coxib-induced prothrombotic state. An in-depth analysis of the off-drug extension data is currently under way. In the meantime, continued follow-up of this cohort of patients will be valuable in understanding the long-term risks associated with rofecoxib.

Risk of Ischemic Cardiovascular Events With the Other Coxibs

Whether or not the cardiovascular risks of rofecoxib is a class effect of COX2 inhibitors is an issue that needs clarification. After all, the various COX2 inhibitors have important structural, pharmacodynamic, and pharmacokinetic differences, as listed in Table 3 (44). Celecoxib, for example, is the least selective of the coxibs; with a COX1:COX2 half-maximal inhibitory concentration ratio of 30, it is only slightly more COX2-selective than diclofenac, which has a ratio of 20. In terms of metabolism, rofecoxib is the only one that it is inactivated by cytosolic reductases. The other coxibs are oxidized by cytochrome P450 enzymes, making them potentially more susceptible to drug-drug interactions. Furthermore, an in vitro study by Walter et al. (45) suggested that coxibs with a sulfone moiety, namely rofecoxib and etoricoxib, enhanced the susceptibility of lipids to oxidative modification through a process unrelated to their COX activity. This pro-oxidant property was not observed with other coxibs and nonselective NSAIDs. Inherent differences like these can potentially translate into differences in in vivo behaviors and clinical outcomes.

In fact, a few observational studies have suggested differences in cardiovascular risk between rofecoxib and celecoxib. In a case-control study by Kimmel et al. (46), the adjusted odds ratios for MI among celecoxib users and rofecoxib users compared with individuals who did not use NSAIDs were 0.43 (95% CI 0.23 to 0.79) and 1.16 (95% CI 0.70 to 1.93), respectively. In another case-control study using data from Kaiser Permanente, Graham et al. (47) showed that the odds ratio for an acute MI and sudden cardiac death among rofecoxib users compared with celecoxib users was 1.47 (95% CI 0.99 to 2.17) if the dose was ≤25 mg/day and 3.58 (95% CI 1.27 to 10.11) if the dose was >25 mg/day. Finally, in a study by Solomon et al. (48) that compared the rates of MI and ischemic stroke in users of nonselective NSAIDs or coxibs (including celecoxib, rofecoxib, and valdecoxib) with those in nonusers, rofecoxib was the only coxib that significantly increased the risk of cardiovascular events. Taken together, these studies suggested that the increased cardiovascular risk seen with COX2 inhibitors was most prominent with, and perhaps limited to, rofecoxib.

On the other hand, some randomized trials only strengthened the notion that adverse cardiovascular events were a class effect of COX2 inhibitors. The APC (Adenoma Prevention with Celecoxib) study was one such trial (10) (Table 2). It randomized 2,035 patients with a history of colorectal neoplasia to receive placebo or celecoxib, either 400 or 800 mg/day. During 3 years of follow-up, celecoxib was associated with a dose-related increase in the composite end point of cardiovascular death, nonfatal MI, stroke, and heart failure, and this effect was independent of concomitant

Table 3 Structures, Pharmacodynamics, and Pharmokinetics of the Various Selective COX2 Inhibitors

	Structure	COX1:COX2 IC_{50}* Ratio	Oral Bioavailability (%)	Half-Life (h)	Metabolism
First-generation coxibs					
Celecoxib	Sulfonamide	30	22–40	2–4	Cytochrome P450
Rofecoxib	Sulfonyl	276	92–93	2–3	Cytosolic reduction
Second-generation coxibs					
Valdecoxib	Sulfonamide	261	83	2.3	Cytochrome P450
Etoricoxib	Sulfonyl	344	100	1	Cytochrome P450
Lumiracoxib	Phenyl acetic acid	433	74	2–3	Cytochrome P450

Adapted and reprinted, with permission, from Fitzgerald et al. (44). *IC_{50} represents the concentration of the drug required to inhibit 50% of enzyme activity.
COX = cyclooxygenase.

Table 4 Cardiovascular Safety Data for Parecoxib/Valdecoxib From Randomized Controlled Trials

Trial	Number of Patients	Patient Characteristics	Intervention	Duration	CV Outcome	Results
CABG surgery trial by Ott et al. (51)	462	Postelective CABG	Parecoxib 40 mg IV q12 h followed by valdecoxib 40 mg PO q12 h vs. IV/PO placebo	Treatment for 14 days; follow-up for 30 days	MI	Nonsignificant ↑ incidence with parecoxib/valdecoxib
					Heart failure	No difference between the 2 groups
					Cerebrovascular event	Nonsignificant ↑ incidence with parecoxib/valdecoxib
CABG surgery trial by Nussmeier et al. (11)	1,671	Postelective CABG	Parecoxib 40 mg IV once, then 20 mg IV q12 h followed by valdecoxib 20 mg PO q12 h vs. IV placebo followed by valdecoxib 20 mg PO q12 h vs. IV/PO placebo (ASA given to all patients post-CABG)	Treatment for 10 days; follow-up for 30 days	Composite of CV death, MI, ischemic stroke, TIA, DVT, and pulmonary embolism	↑ Risk with parecoxib + valdecoxib combination compared with placebo: HR 3.7 (1.0–13.5) Trend toward ↑ risk with placebo + valdecoxib combination compared with placebo: HR 2.0 (0.5–8.1)

CABG = coronary artery bypass grafting; DVT = deep venous thrombosis; IV = intravenous; PO = per os (oral); q12 h = every 12 hours; TIA = transient ischemic attack; other abbreviations as in Tables 1 and 2.

use of aspirin or lipid-lowering medication. Notably, these findings contrasted with those of other studies, including CLASS (celecoxib vs. ibuprofen or diclofenac) and 3 unpublished studies, namely PreSAP (Prevention of Colorectal Sporadic Adenomatous Polyps; celecoxib vs. placebo), ADAPT (Alzheimer's Disease Anti-inflammatory Prevention Trial; celecoxib vs. naproxen or placebo), and SUCCESS-1 (the first Successive Celecoxib Efficacy and Safety Study; celecoxib vs. naproxen or diclofenac), all of which did not show any statistical difference in the risk of cardiovascular thrombotic events between celecoxib and a comparator nonselective NSAID and/or placebo (49) (Table 2). It should be emphasized, however, that like the APPROVe study, the strength of the APC trial lay in its use of a placebo as control and its treatment and follow-up duration of over 24 months. In a recent meta-analysis of randomized trials of celecoxib, Caldwell et al. (50) concluded that celecoxib significantly increased the risk of MI when compared with placebo (odds ratio 2.26, 95% CI 1.0 to 5.1) or when compared with placebo, diclofenac, ibuprofen, and paracetamol (odds ratio 1.88, 95% CI 1.15 to 3.08), but did not significantly increase the risk of other outcomes such as cardiovascular death and stroke.

Analogous to the results of the APPROVe and APC studies, 2 trials of valdecoxib and its pro-drug, parecoxib, for pain management after elective CABG questioned the safety of these drugs in high-risk patients (11,51) (Table 4). The larger of the 2 studies randomized 1,671 patients to one of three 10-day treatment arms: 1) intravenous parecoxib followed by oral valdecoxib; 2) intravenous placebo followed by oral valdecoxib; or 3) placebo. All patients received low-dose aspirin and were allowed to receive opiates postoperatively as needed. During only 30 days of follow-up, cardiovascular events, including MI, cardiac arrest, stroke, and pulmonary embolism, occurred more frequently in patients who received parecoxib and valdecoxib than in those who received placebo (2.0% vs. 0.5%, $p = 0.03$).

Lumiracoxib was evaluated in the TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial) study (52) (Table 5). This was the first published study of coxibs in arthritis patients that prospectively evaluated predefined cardiovascular events along with gastrointestinal events. Over 18,000 patients were randomized to lumiracoxib (at doses 2 to 4 times higher than the recommended dose for OA), naproxen, or ibuprofen. Patients who were deemed high-risk for cardiovascular disease were started on low-dose aspirin before enrollment. After 1 year, the incidence of the APTC end point was slightly, but not significantly, higher in the lumiracoxib group compared with the nonselective NSAID group; this lack of statistical difference was not influenced by the use or nonuse of aspirin. Similarly, for MIs, no significant difference was found between lumiracoxib users and the combined nonselective NSAID group; however, there was an excess of events in the lumiracoxib arm, which became more prominent when naproxen was used as the comparator. Three points about this trial deserve mention. First, although it was a large trial, it was still insufficiently powered to detect significant differences in MI among non-aspirin users. Second, patients on low-dose aspirin had at least a 2-fold higher number of composite vascular events than did non–aspirin-treated patients, whether they were assigned to lumiracoxib or to nonselective NSAIDs. Counterintuitive as it may seem, this could reflect either an inability of aspirin to provide cardioprotection against lumiracoxib and NSAIDs, or the potentially higher baseline risk of those being treated with aspirin. Finally, there was an issue about hepatotoxicity. Transaminase elevations of more than 3-fold occurred in more patients on lumiracoxib than in those on the 2 nonselective NSAIDs (hazard ratio [HR] 3.97, 95%

Table 5 Cardiovascular Safety Data for Etoricoxib and Lumiracoxib From Randomized Controlled Trials

Trial	Number of Patients	Patient Characteristics	Intervention	Duration	CV Outcome	Results
Pooled analysis of etoricoxib phase IIB/III trials (54)	≈6,700	RA, OA, chronic low back pain	Etoricoxib vs. placebo	3 months	Thrombotic CV events	RR with etoricoxib 1.11 (0.32–3.81)
			Etoricoxib vs. non-naproxen NSAID	36 months	Thrombotic CV events	RR with etoricoxib 0.83 (0.26–2.64)
			Etoricoxib vs. naproxen	30 months	Thrombotic CV events	Trend toward ↑ risk with etoricoxib: RR 1.70 (0.9–3.18)
EDGE (54)	7,111	OA	Etoricoxib 90 mg/day vs. diclofenac 150 mg/day	Mean of 9 months (maximum of 16 months)	Thrombotic CV events	No difference between the two groups: RR 1.01 (0.65–1.58)
					APTC end point	No difference between the two groups: RR 0.99 (0.58–1.67)
EDGE II (54)	≈4,090	RA	Etoricoxib 90 mg/day vs. diclofenac 150 mg/day	Mean of 19 months (maximum of 34 months)	Thrombotic CV events (predefined)	Trials are ongoing
MEDAL (54)	≈23,450	RA, OA	Etoricoxib OA: 60 mg/day RA: 90 mg/day vs. diclofenac 150 mg/day	Mean of 20 months (maximum of 40 months)		
TARGET (52)	18,325	OA	Lumiracoxib 400 mg/day vs. naproxen 500 mg 2x/day vs. ibuprofen 800 mg 3x/day (ASA allowed)	1 yr	APTC end point (predefined)	No difference among the three groups
						Lumiracoxib vs. nonselective NSAIDs: HR 1.14 (0.78–1.66)
						Lumiracoxib vs. naproxen: HR 1.46 (0.89–2.37)
						Lumiracoxib vs. ibuprofen: HR 0.76 (0.41–1.40)
					MI	Trend toward ↑ risk with lumiracoxib compared with naproxen
						Lumiracoxib vs. nonselective NSAIDs: HR 1.31 (0.70–2.45)
						Lumiracoxib vs. naproxen: HR 1.77 (0.82–3.84)
						Lumiracoxib vs. ibuprofen: HR 0.66 (0.21–2.09)
					Heart failure	Less frequent in lumiracoxib group than nonselective NSAID group: OR 0.71 (0.39–1.3)
					Systolic and diastolic BP elevation	Less degree of elevation with lumiracoxib compared with nonselective NSAIDs

BP = blood pressure; OR = odds ratio (numbers in parentheses represent the 95% interval); other abbreviations as in Tables 1 and 2.

CI 2.96 to 5.32). Whether or not this was a dose-dependent phenomenon related to supratherapeutic doses of lumiracoxib remains unanswered. Nonetheless, on the basis of the above findings, it is difficult to justify the use of lumiracoxib at this time (53). For patients not taking aspirin, the absolute reduction of 0.72% in ulcer complications is offset by an excess of 2.0% of liver function test abnormalities and an excess of 0.17% of MI if naproxen is used as the comparator NSAID. For patients taking low-dose aspirin, it is even harder to justify lumiracoxib because the benefit of ulcer complication reduction is lost.

Etoricoxib and lumiracoxib are the 2 newest coxibs that have yet to be examined for approval by the FDA. Clinical trials of etoricoxib are ongoing and include EDGE II (Etoricoxib vs. Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness Trial in Rheumatoid Arthritis

Patients), which included 4,000 patients with RA, and MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term Study), which included 23,500 patients with RA and OA. The data from these 2 studies will be combined with those from the recently completed EDGE trial, another trial of etoricoxib involving 7,111 patients, and an analysis of predefined cardiovascular outcomes will be made. Together, the data from these trials will form the largest NSAID analysis ever designed (54) (Table 5).

Other Potential Adverse Cardiovascular Effects of Coxibs

Although nonselective NSAIDs have been associated with an increased risk of congestive heart failure (CHF) or worsening CHF (55,56), it is less clear whether COX2 inhibitors share the same risk. At least 2 observational studies have suggested that this risk is associated with rofecoxib but less so with celecoxib (57,58). One of them was a population-based cohort study that compared the rates of hospitalization for CHF among NSAID-naive elderly individuals who were started on rofecoxib (n = 14,583), celecoxib (n = 18,908), and nonselective NSAIDs (n = 5,391), and a randomly selected control group of non-NSAID users (n = 100,000). Compared with control patients and after adjustment for potential confounders, the relative risk (RR) of admission for CHF was significantly higher in those who received rofecoxib (RR 1.8, 95% CI 1.5 to 2.2) and nonselective NSAIDs (RR 1.4, 95% CI 1.0 to 1.9), but not in those who received celecoxib (RR 1.0, 95% CI 0.8 to 1.3). In the APPROVe study, CHF and pulmonary edema occurred earlier (about 5 months after starting the study drug) and at a higher rate in patients who took rofecoxib than in the control group (HR 4.61, 95% CI 1.50 to 18.83) (8).

Non-steroid anti-inflammatory drugs have also been associated with blood pressure elevation and lower extremity edema (59). Coxibs may share these risks, although once again, the greatest risk seems to be with rofecoxib. In a meta-analysis of 19 randomized trials involving 45,461 patients, the weighted mean difference in systolic blood pressure was +3.85/+1.06 mm Hg and +2.83/+1.34 mm Hg when coxibs were compared with placebo and nonselective NSAIDs, respectively (60). Among the different coxibs that were compared with placebo, the largest increase in systolic blood pressure was with rofecoxib (+5.66 mm Hg vs. +2.60 mm Hg with celecoxib). Rofecoxib also resulted in a statistically significant increase in the risk of hypertension compared with placebo (RR 2.63, 95% CI 1.42 to 4.85), whereas celecoxib (RR 0.81, 95% CI 0.13 to 5.21) and etoricoxib (RR 1.23, 95% CI 0.44 to 3.44) did not. Data from the CLASS and APPROVe trials suggested similar findings. In the CLASS trial, the incidence of hypertension was lower in the celecoxib group compared with the nonselective NSAID group (1.7% vs. 2.3%, $p < 0.05$), whereas the incidence of peripheral edema was comparable between the 2 groups (2). The APPROVe study, on the other hand, suggested an increased risk of hypertension and peripheral edema with rofecoxib compared with nonselective NSAIDs (8). Like celecoxib in the CLASS trial, lumiracoxib was not implicated in blood pressure elevation in the TARGET trial; in fact, nonselective NSAIDs were associated with significantly higher mean changes in systolic and diastolic blood pressure compared with lumiracoxib (systolic blood pressure: +2.1 mm Hg vs. +0.4 mm Hg, $p < 0.0001$; diastolic blood pressure: +0.5 mm Hg vs. −0.1 mm Hg, $p < 0.0001$) (52).

Conclusions

Drawing conclusions from the numerous studies on coxibs and their cardiovascular risk obviously has not been straightforward. Although it is understandable why clinical trials on arthritis patients would use nonselective NSAIDs as comparators, the lack of a placebo arm complicates the interpretation of the results, especially because NSAIDs may have cardiovascular effects themselves. In addition, most of the data we have on coxibs were derived from post hoc and non-prespecified analyses of randomized trials. We are still in need of randomized controlled trials that are purposely designed and adequately powered to examine the cardiovascular effects of these drugs. One such trial has been planned for celecoxib, PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen), which hopes to assess the relative safety of these drugs in about 21,000 patients with OA or RA and known CAD or multiple risk factors for CAD over a duration of 2 years (61).

Amidst the multitude of studies on coxibs, one thing we have learned is what specific questions to ask. Although the current data have their limitations, fortunately it is possible to draw a fair number of conclusions to answer some of these questions.

First, are all coxibs the same? We do not believe so. Although there are good data from randomized trials of rofecoxib, valdecoxib/parecoxib, and celecoxib to suggest that each of these drugs can result in adverse cardiovascular events (as though to suggest a class effect), there are likewise numerous studies that indicate different degrees of risk associated with different coxibs. The latter has been underscored by studies such as CLASS, PreSAP, ADAPT, and SUCCESS-1, which have shown no increased risk with celecoxib, and observational studies that have shown differences in risks between rofecoxib and celecoxib. That these differences are related to the COX2 selectivity of the drug or certain moieties within its chemical structure has been suggested but cannot fully account for the findings of the randomized trials. For example, of the various coxibs, lumiracoxib is the most COX2 selective, followed by rofecoxib and then celecoxib. The associated cardiovascular risks seen in the TARGET (lumiracoxib), VIGOR and APPROVe (rofecoxib), and CLASS and APC (celecoxib) trials, however, did not line up in quite the same order.

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Unfortunately, there are no clinical trials that have made head-to-head comparisons of the various coxibs on which we can substantiate this idea of a differential risk. It is also important to point out that as much as we have scrutinized the different coxibs, similar emphasis should be placed on the impact of different doses on outcomes. The APC trial showed quite clearly that the adverse events associated with celecoxib were dose-dependent. In this light, concerns about the safety of lumiracoxib in the TARGET trial, and most other coxibs for that matter, may be attenuated if lower doses are used.

Second, how should the cardiovascular risk profile of a patient affect our decision to use or not use a coxib? When the absolute risk increase in cardiovascular events is expected to be high with coxib use, as in a patient with CAD or multiple risk factors for CAD, it is but prudent to avoid a coxib. For the young, low-risk individual, the scenario is less clear. The absolute risk increase in events may be lower, but the relative risk increase can potentially be greater and still reach magnitudes of unacceptability. This is a specific issue that needs clarification by well-designed studies.

Third, is it beneficial to add aspirin when prescribing a coxib to a patient with an intermediate or high cardiovascular risk profile? Although the intuitive answer is yes, once again, the clinical trials do not provide us with a straightforward answer. The post hoc analysis of the APC data showed that patients who took aspirin did not have lower rates of cardiovascular events than those who did not take aspirin. Similarly, in the APPROVe trial, the increased cardiovascular risk experienced by the rofecoxib group did not seem to be influenced by baseline or subsequent use of aspirin. Findings such as these suggest that the adverse outcomes from coxib use might not be solely a consequence of COX2 inhibition (or a thromboxane-prostacyclin imbalance), and other mechanisms might be at play. What is perhaps clearer is the finding that when aspirin is taken together with a coxib, the gastrointestinal safety advantage of the coxib over a nonselective NSAID is lost. This was seen at least in the CLASS and TARGET trials.

Finally, is there still a place for coxibs in our scheme of managing patients with pain syndromes? Are there safer but equally efficacious alternatives? We believe that coxibs will continue to be clinically useful, although in a very select group of patients. These are the individuals who continue to require nonsteroidal anti-inflammatory treatment despite optimization of other modalities (e.g., disease-modifying drugs for RA and analgesics, physical therapy, and physical aids for OA), have a low cardiovascular risk profile, and have a relatively high gastrointestinal bleeding risk. Although the vast majority of trials that compared nonselective NSAIDs with coxibs for pain control did not show superiority of the latter, in clinical practice, the response to pain management varies from individual to individual, and it is not uncommon to have a patient who reports better pain relief with a coxib.

Currently, the impetus for avoiding coxibs is the potential to cause cardiovascular harm. Three important points arise from this statement. First, we actually lack definitive data about where the various nonselective NSAIDs, the presumed alternatives to coxibs, stand in terms of cardiovascular safety. This is because there has been no long-term placebo-controlled trial of conventional NSAIDs designed to evaluate cardiovascular outcomes. The vast majority of observational studies, however, have not shown any significant cardiovascular consequence from nonselective NSAID use, with the exception of naproxen, which has been implicated to be mildly cardioprotective by a few studies. A recent meta-analysis of placebo-controlled randomized trials also failed to show any significant cardiovascular effect of nonselective NSAIDs, including nabumetone, ibuprofen, indomethacin, diclofenac, and even naproxen, except possibly in trials of Alzheimer's disease, in which there was a nonsignificant trend toward increased events (62). Second, certain NSAIDs, such as ibuprofen, can blunt the antiplatelet effect of aspirin, presumably by binding to COX1 and blocking the channel that aspirin must traverse to bind COX1 (63). In view of this, it has been recommended that if aspirin and an NSAID are to be taken on a regular basis, the soluble form of aspirin should be ingested 2 hours before the NSAID (64). This type of interaction becomes essentially irrelevant when aspirin is combined with a coxib because COX2 is not expressed in mature platelets. Finally, if a decision is made to avoid a coxib, the combination of an NSAID with a proton pump inhibitor (PPI) may be just as safe for the upper gastrointestinal tract (65), but perhaps not so for the lower gastrointestinal tract, in which a PPI is not expected to provide any protection (67). A clear advantage of using a nonselective NSAID/PPI combination is its lower cost compared with a coxib, especially if over-the-counter equivalents (e.g., naproxen or ibuprofen plus omeprazole) are used. In patients with high cardiovascular risk who need to be on aspirin, more complex polypharmacy-type combinations such as coxib/aspirin/PPI and nonselective NSAID/aspirin/PPI have been suggested but have not been compared directly (66).

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