

# Cyclooxygenase-2 Inhibitors, Nonsteroidal Anti-inflammatory Drugs, and Cardiovascular Risk

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## KEYWORDS

- Cyclooxygenase-2 inhibitors • Cardiovascular disease
- Thrombosis

Cyclooxygenase-2 (cox-2) inhibitors, also known as coxibs, were introduced with the promise that they would provide pain relief similar to that of traditional nonsteroidal anti-inflammatory drugs (NSAIDs) but would be better tolerated with lower risk for gastrointestinal (GI) side effects. Although coxibs were associated with lower GI risk, experimental and observational data raised the specter of increased cardiovascular risk associated with this class of drugs. When a randomized controlled trial of rofecoxib for colonic polyp prevention was stopped in September 2004 because of a twofold risk for cardiovascular events, the entire class of agents became the subject of intense scrutiny, culminating in withdrawal of two coxibs from the market and a US Food and Drug Administration (FDA)-mandated black-box warning on the remaining agent. Nevertheless, coxibs remain an important part of the pain-management armamentarium for patients who have osteoarthritis, rheumatoid arthritis, and various other conditions. This article describes the pharmacologic and biologic basis of cardiovascular risk associated with coxibs, summarizes the evidence for cardiovascular risk associated with cox-2 inhibitors, and weighs the risks and potential benefits of pain management with these agents.

Analgesics are among the most commonly used medications in the United States and among the

most frequently prescribed medications to patients older than 65 years of age. It has been estimated that more than 70 million NSAID prescriptions are written per year in the United States. Moreover, NSAIDs have been potentially implicated in thousands of deaths and an even greater number of hospitalizations, primarily because of an excess risk for GI bleeds or renal impairment. Treatment of nonsteroidal-related GI side effects has been estimated to account for up to one third of the cost of arthritis therapy. Cyclooxygenase-2 inhibitors were designed and introduced in an attempt to reduce the potential GI risk of traditional NSAIDs. Their adoption was driven by the enormous profit potential in safer analgesics, and a medical community and consumers eager to reduce the GI risks with similar pain relief.

## PHARMACOLOGY OF CYCLOOXYGENASE-2 INHIBITORS

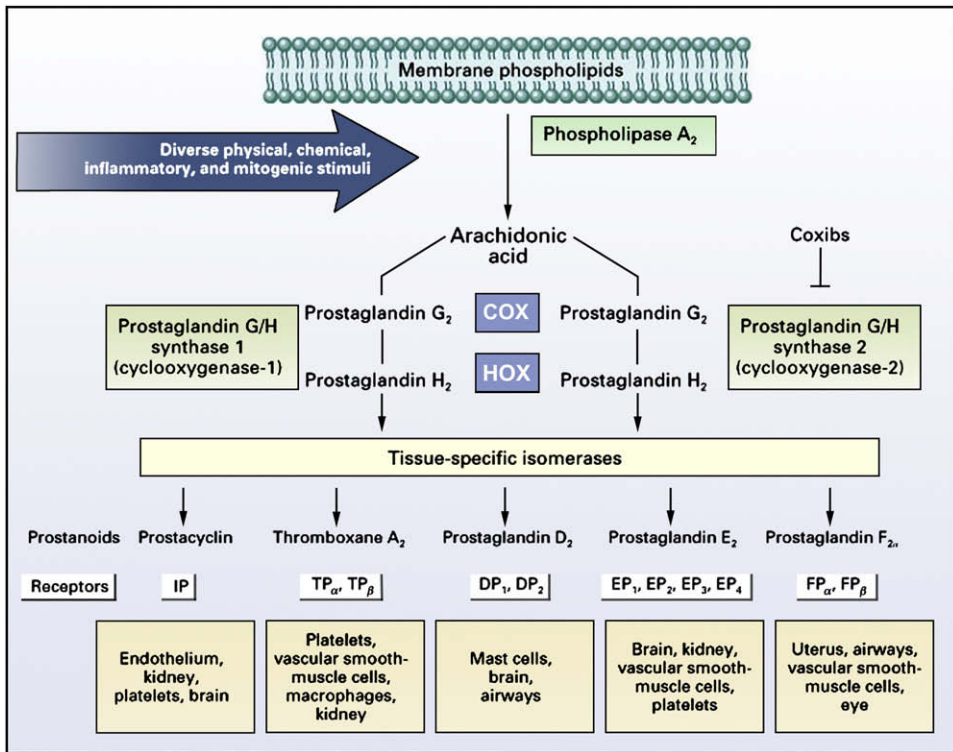
Cyclooxygenase-2 inhibitors and traditional NSAIDs inhibit enzymes that convert prostaglandins to tissue-specific isomerases (Fig. 1). The prostaglandin cascade begins with the release of arachidonic acid from membrane phospholipids through actions of lipases (primarily phospholipase A2 type).<sup>1,2</sup> Thereafter, four distinct pathways contribute to oxidizing arachidonic acid to

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**Fig. 1.** Production and actions of prostaglandins and thromboxane. (From Fitzgerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;345:433–42; with permission. Copyright © 2001, Massachusetts Medical Society.)

form eicosanoids, which serve numerous roles in biologic systems and disease, including cardiovascular, GI, blood coagulation, nervous, and reproductive systems. One of the four eicosanoid-forming pathways is that of prostaglandin G/H synthase, otherwise known as the cyclooxygenase (COX) enzyme. The enzyme converts arachidonic acid into prostaglandin G<sub>2</sub> and subsequently to prostaglandin H<sub>2</sub>. Specific eicosanoids formed subsequent to this reaction are termed prostanoids, referring to various prostaglandins and thromboxane compounds. The distribution of prostanoid types is determined by the cell category in which the prostanoids are produced and tissue-specific isomerases contained within.<sup>3</sup> For example, endothelial cells express PGI synthase and produce the antithrombotic vasodilator prostanoid PGI<sub>2</sub>, or prostacyclin. Platelets express PGE synthase, and are capable of forming the inflammatory, prothrombotic PGE<sub>2</sub> prostanoid.

The cyclooxygenase enzyme exists as two distinct isoenzymes, the COX-1 and COX-2 isoenzymes, with differential expression in various tissues.<sup>4</sup> It was originally believed that the COX-1 isoenzyme functioned primarily as a housekeeping enzyme in the cytoprotection of gastric mucosa, regulation of renal blood flow, and platelet

aggregation. This enzyme is constitutively expressed, detectable in the bloodstream, and is the only isoenzyme expressed in platelets. In contrast, COX-2 levels and activities are normally undetectable in blood vessels, but are rapidly up-regulated on exposure to cytokines, endotoxins, tumor promoters, and mitogens, giving rise to the notion that this enzyme mediates production of inflammatory response prostanoids.<sup>5</sup> The mechanistic distinction between COX-1 and COX-2 isoenzymes is not that clear-cut. Although COX-1 is the predominant isoenzyme in normal gastric mucosa, there are increasing data to support that COX-2 mRNA and protein are either constitutive or inducible during acute stages of gastric erosion and ulceration in areas of the GI tract.<sup>6,7</sup> Similarly, it is not just the COX-2 isoenzyme that is inducible during inflammation; COX-1 induction occurs in arthritic synovia or in atherosclerotic plaques.<sup>8,9</sup>

COX-1 products, which include PGI<sub>2</sub> and PGE<sub>2</sub>, maintain GI system integrity by decreasing gastric acid secretion, increasing the thickness of the gastric mucus layer, enhancing blood flow to mucosal tissues, and stimulating bicarbonate secretion.<sup>10,11</sup> PGE<sub>2</sub> in particular is responsible for gastric mucosal secretion through activation of cAMP in gastric epithelial cells.<sup>12</sup> Blockade of

COX-1 prevents formation of the cytoprotective prostaglandin PGE<sub>2</sub>, and in addition to reduced production of thromboxane A<sub>2</sub> (TxA<sub>2</sub>) in platelets, increases the risk for gastric mucosal damage and bleeding.<sup>13</sup> Aspirin and traditional NSAIDs, which inhibit COX-1 and COX-2 enzymes, thus increase the risk for gastric mucosal injury.

The development of numerous NSAIDs that block both COX isoenzymes flourished in the 1980s, resulting in various compounds differing in their relative affinity for and blockade of COX-1 versus COX-2 and their anti-inflammatory actions. Concerns of hemorrhagic risk of therapeutic agents that nonselectively block COX-1 and COX-2, with subsequent adverse GI outcomes,<sup>14</sup> led to the idea that selective blockade of the COX-2 enzyme would mitigate negative GI effects<sup>15</sup> and thus lead to drugs with the promise of fewer adverse GI effects while still decreasing inflammation and pain.

The coxibs were approved based on their reduced rates of endoscopically visualized gastroduodenal ulcerations in comparison to equivalent doses of traditional NSAIDs. These approvals were based on three year-long and one short-term outcome study examining incidence of serious GI complications in larger populations.<sup>16–18</sup>

Tertiary structure differences of COX isoenzymes account for pharmacologic disparities between COX-1/COX-2 nonselective and COX-2 selective agents. A hydrophobic pocket in the binding channel of COX-2 is absent in COX-1.<sup>4,19</sup> Selective inhibitors of COX-2 have side chains that fit within the hydrophobic pocket but are too large to block COX-1 with equally high affinity. The interaction of all NSAIDs and coxibs with COX-1 and COX-2 is therefore conditioned by their molecular structure. There is no absolute selectivity for one isoform versus another, and the relative affinities to the two isoforms are just as variable within the NSAID and coxib classes as between them. COX-2 selectivity is best described as a continuous scale on which the agents can be ranked. The concentration of drug required to inhibit the activities of COX-1 and COX-2 enzymes by 50% is termed the IC<sub>50</sub>. The COX-1 IC<sub>50</sub> value:COX-2 IC<sub>50</sub> value ratio can be used to determine a selectivity index.<sup>20</sup> A value less than 1 indicates the drug is more COX-1 selective, whereas a value greater than 1 indicates the drug is more COX-2 selective.<sup>21</sup> First-generation coxibs include celecoxib and rofecoxib, which are the least COX-2 selective of the coxibs. The second-generation coxibs, such as etoricoxib and lumiracoxib, are more selective for COX-2 than rofecoxib, an agent possessing higher relative COX-2 affinity than celecoxib (Table 1).<sup>22</sup> Evaluation of traditional NSAIDs has

**Table 1**  
Pharmacologic differences among COX-2 inhibitors

Compound	COX-1:COX-2 IC <sub>50</sub> Ratio <sup>a</sup>	Half- Life (h)
First generation		
Celecoxib	6	6–12
Rofecoxib	38	15–18
Second generation		
Valdecoxib	28	6–10
Etoricoxib	105	20–26
Lumiracoxib	515	2–6

<sup>a</sup> Measured with human whole blood assay; the concentration required to inhibit COX activity by 50%.

Data from Coruzzi G, Venturi N, Spaggiari S. Gastrointestinal safety of novel nonsteroidal antiinflammatory drugs: selective COX-2 inhibitors and beyond. *Acta Biomed.* Aug 2007;78(2):96–110.

shown that some compounds, including diclofenac, nimesulide, and nabumetone, display similar selectivity as that of celecoxib.<sup>23</sup> Similarly, coxibs vary widely in their duration of action (half-life), such that etoricoxib possesses the longest half-life and celecoxib and lumiracoxib have shorter half-lives. Selectivity ratio of various coxibs is highly variable, depending on the assay and experimental conditions used. Additionally, differences in selectivity may not correlate with therapeutic efficacy after dosing.

## GASTROINTESTINAL EFFECTS OF COXIBS

Because coxibs were developed with the promise of a lower risk for GI side effects, much of the initial clinical research on coxibs sought to document the beneficial GI profile of these agents compared with traditional NSAIDs. In the VIGOR trial,<sup>16</sup> rofecoxib was associated with approximately a 50% reduction in the risk for serious lower GI events. Similarly, in the CLASS trial<sup>17</sup> celecoxib was associated with fewer upper GI tract complications compared with patients treated with NSAIDs. This benefit was completely absent in the patients who were taking low-dose aspirin for cardiovascular reasons, however, which suggests that concomitant use of aspirin—even low-dose aspirin—simultaneously with coxibs may actually attenuate their potential GI benefits. Although celecoxib was associated with less upper GI bleeding in the CLASS study after 6 months, further follow-up out to 1 year (which was reported to the FDA but not published in the initial manuscript) failed to show a clear-cut benefit of celecoxib use.

Although the GI benefits of coxibs in comparison to traditional NSAIDs have been supported by several studies and with several agents, the GI safety of coxibs over placebo has not been as clear. In the APPROVe trial,<sup>24</sup> rofecoxib was associated with an increased risk for GI ulcers and bleeding compared with placebo, suggesting that although coxibs may reduce the risk for GI side effects compared with traditional NSAIDs, the risk is not nullified when compared with placebo. Interestingly, hospital admissions for GI hemorrhage increased around the time of the introduction of celecoxib and rofecoxib, and it has been postulated that this increased observed incidence may be directly related to the introduction of the coxib medications with resultant overprescribing, preferential prescription to high-risk subjects, and concomitant use of low-dose aspirin.<sup>25</sup>

Other potential GI benefits, supported by experimental literature and early clinical trials, have also been attributed to coxibs. COX-2 is expressed at all stages of human colon carcinogenesis, has been shown to be a promoter of intestinal tumorigenesis, and may be an important promoter of tumorigenesis in various epithelial carcinomas.<sup>26</sup> Overexpression of COX-2 in experimental models results in tumor production of angiogenic factors and proteolytic enzymes and prostaglandin-mediated resistance to apoptosis. These experimental findings led to enormous interest in the therapeutic potential for coxibs to prevent cancer and provided a rationale for numerous chemoprevention trials, particularly in the arena of colon cancer. In the Familial Adenomatous Polyposis (FAP) trial, celecoxib in doses of 400 mg twice daily resulted in a 28% reduction in the number of colorectal polyps in patients at high risk for development of colon cancer.<sup>27</sup> This trial was the basis of additional trials testing coxibs more broadly for colon cancer prevention—trials that ultimately led to a greater understanding of the cardiovascular risk associated with coxibs.

### PHARMACOLOGIC BASIS OF CARDIOVASCULAR RISK

Before the existence of compelling clinical data suggesting increased cardiovascular risk associated with coxibs, experimental data had raised concerns of increased risk, especially that of thrombosis. The mechanistic support for this risk came from experimental data, which suggested that coxibs might lead to an imbalance between two downstream prostanoids, thromboxane and prostacyclin.

Thromboxane A<sub>2</sub> (TxA<sub>2</sub>) is formed in the platelet by the action of thromboxane synthase. It

possesses potent vasoconstrictor activity, facilitates cholesterol uptake, induces proliferation of vascular smooth muscle cells, and stimulates platelet aggregation. TxA<sub>2</sub> binds to a G-protein-coupled receptor on platelet plasma membranes. Ultimately, TxA<sub>2</sub> induces a conformational change of the integrin  $\alpha 2\beta 3$ , which mediates the final steps in platelet activation, resulting in platelet binding to fibrinogen and fibronectin.

Conversely, prostaglandin I<sub>2</sub> (PGI<sub>2</sub>, or prostacyclin) causes vasodilation, decreases platelet aggregation, reduces cholesterol uptake, inhibits vascular smooth muscle cell proliferation,<sup>22</sup> and may have a cardioprotective role in the vasculature in the context of ischemia-reperfusion injury.<sup>28</sup>

Recent studies have demonstrated that genomic or pharmacologic removal of prostacyclin led to platelet-dependent and platelet-independent induction of thrombosis, plaque destabilization, or atherogenesis.<sup>29–32</sup> In murine models, deficiency of PGI<sub>2</sub> signaling did not result in spontaneous thrombosis, but once the thrombotic process was induced by endothelial damage, it proceeded more vigorously than in mice with intact PGI<sub>2</sub> function.<sup>33</sup>

The notion that coxibs might be associated with increased risk for thrombosis in humans originated from a series of experiments by Fitzgerald and colleagues<sup>34,35</sup> showing that administration of coxibs to normal volunteers was associated with a reduction in prostacyclin production in a dose-dependent fashion without changes in thromboxane. By selectively blocking production of the vasodilatory and platelet-inhibitory properties of prostacyclin, coxibs may create a prothrombotic environment dominated by TxA<sub>2</sub>.<sup>2,5,36</sup> This alteration in the balance between these two prostanoids allows TxA<sub>2</sub> to function unopposed, and has been proposed to lead to a more thrombogenic state, which under the correct clinical circumstances might result in pathologic thrombosis (Fig. 2).

Opponents to the prothrombotic hypothesis argue that murine models do not adequately translate to human models when it comes to inhibition of prostacyclin production, as its synthesis is not completely blocked in humans as it is in mice. COX-2 inhibitors depress PGI<sub>2</sub> by 50% to 70% in humans.<sup>35,37</sup> Nonetheless, data suggest that a mere 50% reduction in prostacyclin production is sufficient to increase susceptibility to thrombotic stimuli.<sup>38</sup> This finding does raise the question, however, whether incomplete blockade of prostacyclin production in humans leads to varying risk profiles between coxibs with differing duration of activity. Another argument opposing the prothrombotic hypothesis involves the source of

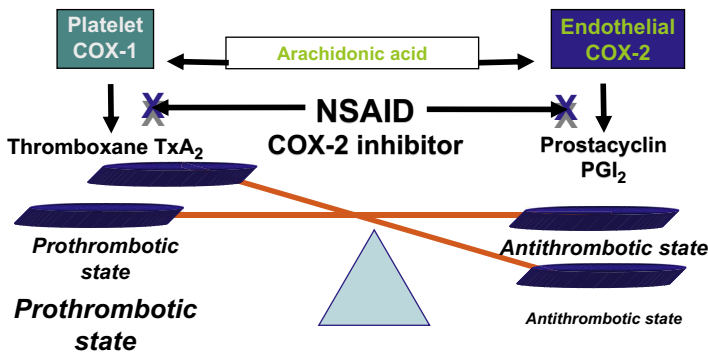


Fig. 2. Mechanism-based Fitzgerald hypothesis of cardiovascular risk for coxibs. (Data from Fitzgerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;345:433–42; and García Rodríguez LA. The effect of NSAIDs on the risk of coronary heart disease: fusion of clinical pharmacology and pharmacoepidemiologic data. *Clin Exp Rheumatol.* 2001;19(6 Suppl 25):S41–4.)

PGI<sub>2</sub>. Biosynthesis of PGI<sub>2</sub> is quantified by the measurement of its urinary metabolite, 2,3 dinor 6-keto PGF<sub>1a</sub>.<sup>34</sup> Rofecoxib and celecoxib were shown to suppress 2,3 dinor 6-keto PGF<sub>1a</sub> to a significant degree.<sup>39,40</sup> Although a good measure of whole-body PGI<sub>2</sub> biosynthesis, measuring urinary metabolites does not allow for quantification of PGI<sub>2</sub> in the vessel wall, and may therefore not reflect COX-2–dependent inhibition of vasculature PGI<sub>2</sub> production. MacAdam and colleagues<sup>35</sup> measured urinary prostacyclin levels in healthy volunteers 6 to 12 hours after a dose of celecoxib or ibuprofen and found that prostacyclin levels were reduced by approximately 80% in patients receiving 400 or 800 mg of celecoxib. Prostacyclin levels were also reduced, but to a somewhat lesser extent, in patients receiving ibuprofen.

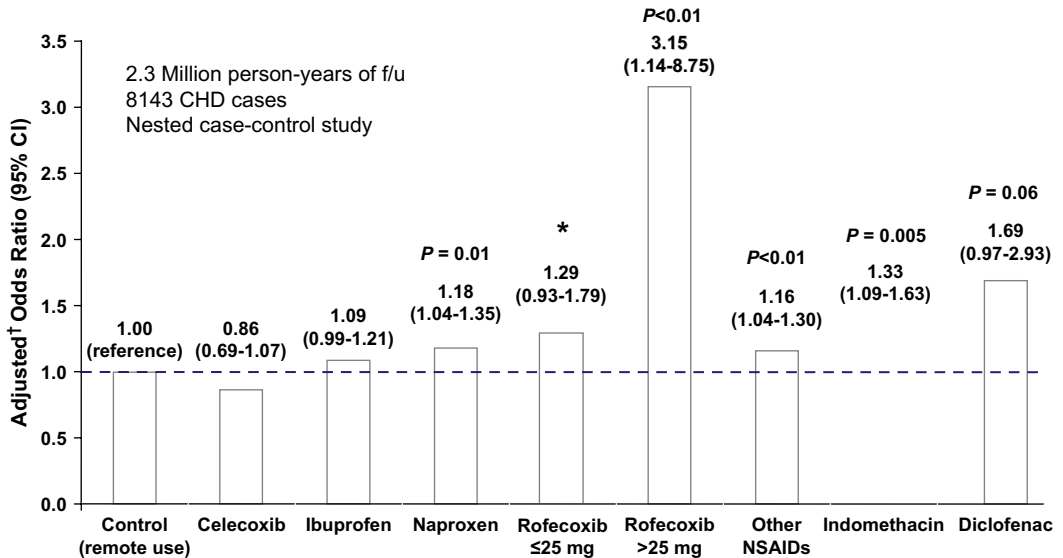
Regardless of the controversies surrounding the prothrombotic hypothesis and the strength of its association with cardiovascular risk, it is recognized that other mechanisms may also contribute to adverse cardiac events with coxibs, including disrupted blood pressure homeostasis. Although the COX-1 isoenzyme is predominant in the kidneys, COX-2 serves to regulate renal blood flow. PGE<sub>2</sub> and PGI<sub>2</sub> increase renal medullary blood flow, which drives diuresis and reduces blood pressure.<sup>41</sup> Inhibition of COX-2 production of PGE<sub>2</sub> induces a reduction in daily urinary sodium excretion by approximately 30%. The retention of sodium and water clinically manifests as increased systemic blood pressure.<sup>42</sup> In patients who have normal renal function, the kidneys increase sodium excretion to compensate for the antinatriuretic effects of the COX inhibitor.<sup>41</sup> This process occurs without significant increases in blood pressure or plasma volume. In patients who have chronic kidney disease, this compensatory mechanism is impaired, leading to increases in blood pressure and edema, in some cases causing heart failure.<sup>43</sup>

In a randomized controlled trial of patients who had osteoarthritis and type II diabetes who were on stable antihypertensive medication, celecoxib,

naproxen, and rofecoxib were associated with 16%, 19%, and 30% incidence of development of hypertension (systolic blood pressure [SBP] >135), respectively, in patients who were previously normotensive.<sup>44</sup> In a case-control analysis of a Medicare population, new-onset hypertension developed in 21%, 23%, and 27% of those prescribed celecoxib, NSAIDs, or rofecoxib, respectively.<sup>45</sup> The increased rates of hypertension induced by rofecoxib were thus significantly higher than with celecoxib or nonselective NSAIDs. The risk was higher in those who had renal or hepatic disease, as well as heart failure. Another study evaluated effects of rofecoxib and celecoxib on clinic SBP in 1094 patients on stable doses of antihypertensives. Rofecoxib induced significant increases in SBP in individuals taking angiotensin-converting enzyme inhibitors and  $\beta$ -blockers, but not in those taking calcium antagonists.<sup>43</sup>

#### OBSERVATIONAL AND CLINICAL TRIALS DATA ON CARDIOVASCULAR RISK ASSOCIATED WITH CYCLOOXYGENASE-2 INHIBITORS

Several early observational studies suggested that rofecoxib might be associated with increased cardiovascular risk. These data came from prescription databases and case-control studies in which rofecoxib has been associated with as high as a fourfold increased risk for cardiovascular events. In the FDA-sponsored Kaiser Permanente study<sup>46</sup> looking at the risk for acute myocardial infarction and sudden cardiac death associated with current use of cox-2 selective and nonselective NSAIDs, similar hazard ratios were observed with virtually all NSAIDs with the exception of rofecoxib in doses greater than 25 mg daily (Fig. 3). Although the hazard ratios associated with indomethacin and diclofenac were greater than 1 and, in the case of indomethacin, statistically significant, rofecoxib use at higher than 25 mg was associated with a threefold increased risk for events. In contrast, much of the observational data associated with



AMI = acute myocardial infarction; SCD = sudden coronary death.

\*P = 0.04 compared with celecoxib.

†Adjusted for age, sex, health plan region, medical history, smoking, and medication use.

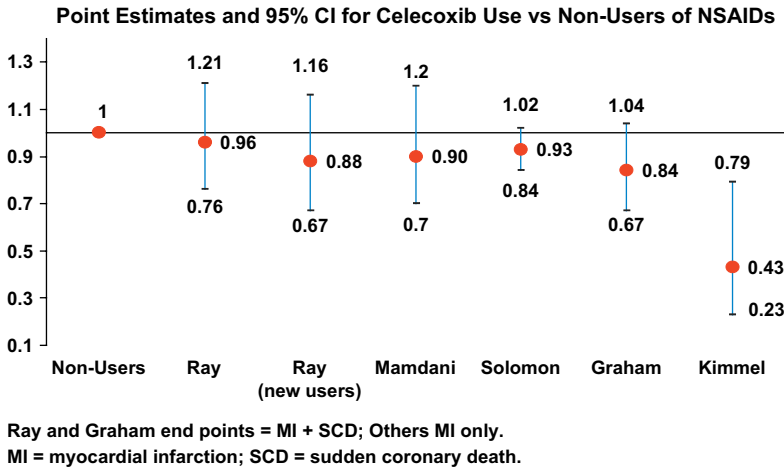
**Fig. 3.** FDA-Sponsored Kaiser Permanente Study: risk for acute myocardial infarction and sudden coronary death with current use of COX-2 selective and nonselective NSAIDs. (Data from Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet* 2005;365(9458):475–81.)

celecoxib was not so unfavorable, with hazard ratios that were almost uniformly less than 1, albeit with wide confidence intervals, when comparing celecoxib use to nonusers of NSAIDs (Fig. 4).

Some important caveats always need to be considered when interpreting the results of observational data. It is difficult or impossible to account for all confounders in observational studies, and especially difficult to address intrinsic biases, including recall bias. Fortunately, the most compelling data for cardiovascular risk associated with coxibs came not from observational studies, but from randomized controlled trials (RCTs). The first such trial to raise concern was VIGOR, which randomized patients who had rheumatoid arthritis to rofecoxib 50 mg a day compared with naproxen 500 mg twice a day. The primary endpoint of the study was GI side effects, which were indeed reduced in patients receiving rofecoxib. The trial demonstrated a higher rate of cardiovascular adverse events in patients receiving rofecoxib compared with those receiving naproxen. Although these data were reported in the initial manuscript, the interpretation was that naproxen was associated with a reduction in risk, and not that rofecoxib was associated with increased risk, and the authors remarked that "...our results are consistent with the theory that naproxen has a coronary protective effect...."<sup>16</sup> This interpretation was only minimally challenged until more definitive data became available years later.

On September 30, 2004, Merck halted the ongoing APPROVe trial and withdrew rofecoxib from the market, citing evidence of increased cardiovascular risk in that study. APPROVe, a colonic polyp prevention study, compared rofecoxib 25 mg to placebo, and followed patients for approximately 3 years. The study was stopped because of a nearly twofold increased risk for cardiovascular death, myocardial infarction, or stroke (Fig. 5). Importantly, APPROVe was testing a relatively common dose of rofecoxib, 25 mg daily, which was the dose being prescribed to most patients who had arthritis. APPROVe was the first direct placebo-controlled evidence of risk associated with rofecoxib that could not be attributed to a benefit associated with an active comparator. The stopping of this trial, and the subsequent withdrawal of rofecoxib from the market, led to an immediate reassessment of all agents in this class.

Several aspects of the APPROVe trial proved subsequently controversial. Safety data in APPROVe were censored 14 days after discontinuation of study drug, with the result that any adverse cardiovascular events occurring after 14 days after study drug would not have been attributed to the drug. This approach has raised several concerns. First, although risk associated with a drug might be expected to dissipate after discontinuation, the timing of that dissipation is unclear, and the most conservative approach



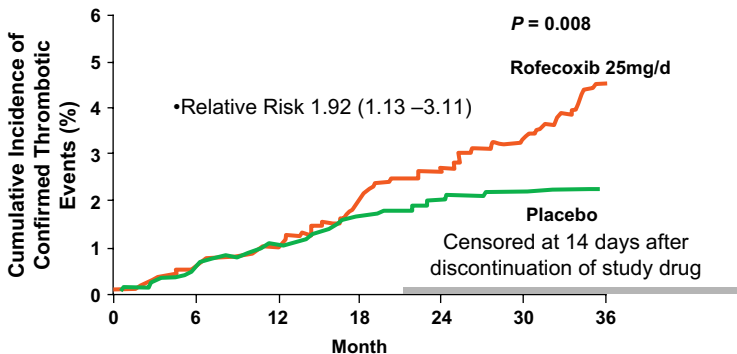
**Fig. 4.** Summary of observational studies of celecoxib and cardiovascular disease. (Data from Ref<sup>46</sup> and Kimmel SE, Berlin JA, Reilly M, et al. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. *Ann Intern Med* 2005;142(3):157–64; Mamdani M, Rochon P, Juurlink DN, et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. *Arch Intern Med* 2003;163(4):481–6; Ray WA, Stein CM, Daugherty JR, et al. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002;360(9339):1071–3; Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation*. 2004;109(17):2068–73.)

generally is to perform an intention-to-treat analysis, wherein adverse event data are counted throughout the duration of follow-up. The APPROVe data have also been used to argue that the risk associated with rofecoxib only began after approximately 18 months of therapy (see Fig. 5). A reanalysis of the APPROVe data based on publicly available data using an intention-to-treat approach has refuted this claim, because it shows curves diverging earlier.<sup>47</sup>

**CELECOXIB CLINICAL TRIALS DATA**

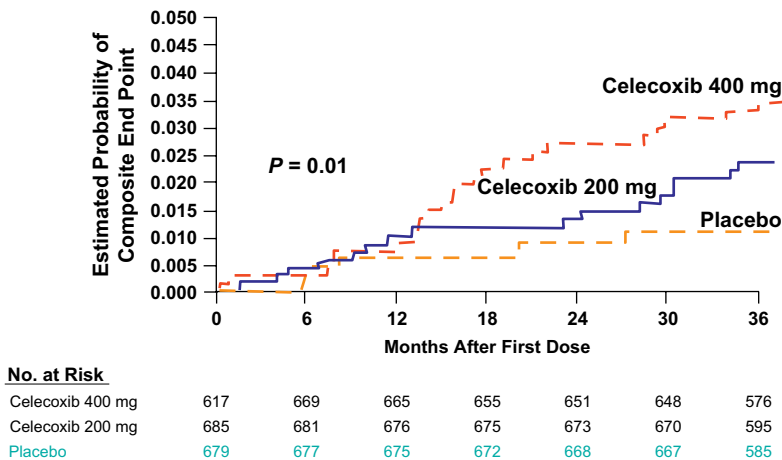
Following termination of the APPROVe study, the data safety monitoring boards of two similar ongoing colon polyp prevention trials, the Adenoma

Prevention with Celecoxib (APC) trial and the PreSAP trial, commissioned an independent review of the cardiovascular data from those trials. Review of the APC data demonstrated a dose-dependent increased risk for a combined endpoint of cardiovascular death, myocardial infarction, stroke, or heart failure associated with celecoxib, with 200 mg twice a day demonstrating a greater than two-fold risk and 400 mg twice a day demonstrating a greater than threefold risk (Fig. 6).<sup>48</sup> On December 17, 2004, these data were made public and the APC and PreSAP trials—and several other trials—were halted. Unlike rofecoxib, celecoxib was not withdrawn from the market. In contrast to APC, the PreSAP trial, which was a similarly designed trial but used a different dose regimen of celecoxib



**Fig. 5.** Cardiovascular data APPROVe APTC events. (From Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352(11):1092–102; with permission. Copyright © 2005, Massachusetts Medical Society.)

No. at Risk							
Rofecoxib	n = 1287	1129	1057	939	938	896	727
Placebo	n = 1299	1195	1156	1079	1042	1001	835



**Fig. 6.** Cardiovascular risk in the APC study. (From Solomon SD, McMurray JJV, Pfeffer MA, et al for the Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352:1071–80; with permission. Copyright © 2005, Massachusetts Medical Society.)

(400 mg once daily), did not demonstrate clear evidence of cardiovascular risk. For the same combined endpoint, PreSAP showed a hazard ratio of 1.3 with 95% confidence interval that ranged from 0.6 to 2.6.<sup>49</sup> Although elevated risk was not observed in PreSAP, these wide confidence intervals suggest that celecoxib may have been associated with as much as a 2.6-fold increased risk or a 40% reduction in risk. Although several potential differences between these two trials, including study population and baseline cardiovascular risk, might account for the differences in the results, dosing interval was the major difference, with PreSAP using a once-daily dose of celecoxib and APC using twice-daily doses.

Review of the APC and PreSAP blood pressure data demonstrated a pattern of blood pressure elevation that paralleled the outcomes data.<sup>49</sup> In APC, 200 mg twice a day and 400 mg twice a day of celecoxib were associated with a significant 2.9 and 5.2 mmHg increase in blood pressure, respectively. In PreSAP, however, no blood pressure elevation was observed. The primary efficacy measures in all three of the colon polyp prevention trials, APC, PreSAP, and APPROVe, were very positive, with between a 25% and 60% reduction in the risk for colonic polyps in patients receiving coxibs.<sup>50–52</sup>

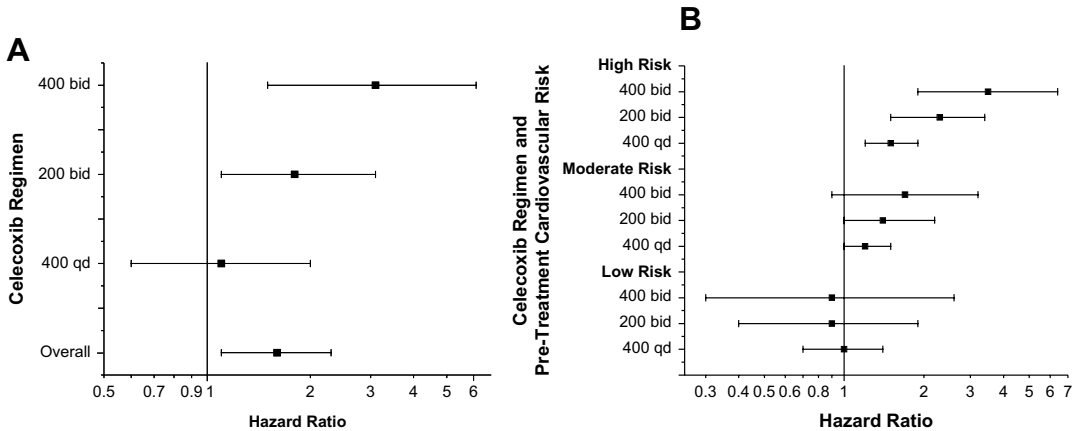
Nearly simultaneous to the reports from the colon cancer prevention trials was the report of an additional study using valdecoxib (Bextra) in patients after bypass surgery.<sup>53</sup> These findings—also demonstrating increased cardiovascular events in the patients receiving coxibs—together with the reports from the colonic polyp prevention trials, were the subject of a special FDA hearing in February 2005. Subsequent to this hearing,

valdecoxib was voluntarily withdrawn from the market, and celecoxib, which remains the only COX-2 inhibitor available in the United States, was given a black-box warning.

The National Institutes of Health–commissioned Cross-Trials Safety Analysis (CTSA) with celecoxib pooled the data from the APC and PreSAP trials with similarly adjudicated data from four other randomized placebo-controlled clinical trials studying the three dose regimens that were studied in APC and PreSAP.<sup>54</sup> These data showed a similar pattern in which the risk increased with dose regimen and was lowest for the 400-mg daily dose (hazard ratio, 1.1; 95% CI, 0.6 to 2.0), intermediate for the 200-mg twice-daily dose (hazard ratio, 1.8; 95% CI, 1.1 to 3.1), and highest for the 400-mg twice-daily dose (hazard ratio, 3.1; 95% CI, 1.5 to 6.1) (Fig. 7A). Moreover, these data demonstrated an interaction with baseline cardiovascular risk, so that patients who had the lowest baseline risk had not only lower absolute risk but also lower relative risk for a celecoxib-related event (see Fig. 7B).

The results of CTSA confirmed the dose-regimen response observed in APC and PreSAP, with another 400-mg once-daily dose trial showing a hazard ratio near 1.0. The importance of dosing interval in celecoxib-related risk is supported by experimental data showing that within about 12 hours of a celecoxib dose, prostacyclin levels, originally diminished, begin to return to normal.<sup>35</sup> It is conceivable, thus, that once-daily dosing might allow enough prostacyclin recovery to attenuate the thrombotic effect of the celecoxib dose, and thus might explain why divided doses might be potentially more toxic than a single dose of the same overall daily amount.





**Fig. 7.** (A) Cardiovascular risk in six randomized placebo-controlled trials comparing celecoxib to placebo (CTSA). (B) Relationship between baseline risk, dose, and celecoxib risk. (From Solomon SD, Wittes J, Finn PV, et al. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. *Circulation* 2008;117(16):2104–13; with permission.)

That baseline risk was an important determinant of celecoxib-related risk suggests that preexisting atherosclerotic disease might be a prerequisite for coxib-related risk, and argues that patients at very low risk for cardiovascular disease in general are probably at very low risk for coxib-related risk. These findings argue for even more caution in using coxibs in patients at increased risk for cardiovascular events.

The CTSA results also need to be considered in light of the high doses of celecoxib tested in these trials, all of which were for conditions other than arthritis. The average daily dose of celecoxib taken by patients who had osteoarthritis was 200 mg daily, much lower than even the lowest 400-mg daily doses in the CTSA trials. The results of these trials thus cannot be extrapolated easily to the lower doses, for which few long-term placebo-controlled data exist.

Since the introduction of rofecoxib, celecoxib, and valdecoxib, other so-called “second-generation” coxibs have emerged. Lumiracoxib, currently approved for use in Canada but not in the United States, was compared with ibuprofen and naproxen in separate randomizations and showed similar rates of cardiovascular outcomes.<sup>18</sup> Similarly, the MEDAL trial,<sup>55</sup> comparing etoricoxib with diclofenac, showed similar rates of adverse cardiovascular events, although the choice of an active comparator in this trial has been criticized because diclofenac, considered a traditional NSAID, has similar COX1:COX2 selectivity as a coxib.

Despite all the available data that have emerged regarding the cardiovascular risk of coxibs over the last several years, the potential cardiovascular

risk associated with traditional NSAIDs remains a major gap in our knowledge. There have been few placebo-controlled trials of NSAIDs in which cardiovascular risk was reported, and most head-to-head comparisons with coxibs have shown similar overall risk. Non-adjudicated data from the ADAPT trial, a study comparing celecoxib or naproxen with placebo in patients at risk for Alzheimer disease, showed clear increased risk associated with naproxen use.<sup>56</sup> Other observational studies have similarly suggested that traditional NSAIDs, which can elevate blood pressure and result in prostacyclin/thromboxane imbalances, can also be associated with increased cardiovascular risk.<sup>57</sup> The ongoing PRECISION trial will prospectively assess the risk of celecoxib compared with ibuprofen and naproxen on cardiovascular risk in patients who have osteoarthritis and rheumatoid arthritis. Still, the lack of a non-NSAID arm will not allow us to interpret the real risks associated with each of these drugs.

## CURRENT RECOMMENDATIONS

Recently the American Heart Association (AHA) put forth a treatment approach for patients who have concomitant arthritis and heart disease.<sup>58</sup> A “stepped care” strategy promotes the short-term use of aspirin, acetaminophen, nonacetylated salicylates, tramadol, and opioid analgesics as first-line therapies. These specific recommendations are controversial because of the paucity of evidence comparing COX-2 inhibitors and opioids with respect to efficacy or adverse effects, lack of long-term studies with opioids, and limited efficacy data and potential side effects with

tramadol. Nonetheless, the AHA recommendations advocate use of agents with the lowest risk for cardiovascular events. Thereafter, progression to other agents, such as NSAIDs and COX-2 inhibitors, should coincide with a risk-benefit consideration at each step. COX-2 inhibitors are reserved as last choice given their cardiovascular hazard. The AHA recommends using the lowest dose of NSAIDs required to control symptoms and adding aspirin 81 mg daily and a proton pump inhibitor (PPI) to COX-2 selective agents in patients at an increased risk for thrombotic events.

The most recent guidelines on management of osteoarthritis of the hip and knee by the American College of Rheumatology (ACR) were published in 2000,<sup>59</sup> just before release of information about cardiovascular risk with coxibs. As such, pharmacologic recommendations following acetaminophen as first line include use of low-dose NSAIDs or coxibs. Patients who have risk factors for GI events should only receive NSAIDs in combination with a PPI or misoprostol. Nonacetylated salicylates were recommended for high-risk patients as an alternative, recognizing risks for ototoxicity and central nervous system toxicity.

In 2002, the American Pain Society (APS) issued guidelines for management of pain in osteoarthritis, rheumatoid arthritis, and juvenile chronic arthritis. These guidelines recommended use of coxibs following acetaminophen before choosing NSAIDs. Again, the most compelling data about cardiovascular risks of coxibs had yet to surface; therefore the ACR and APS guidelines will likely be updated.

### CLINICAL CONSIDERATIONS

A treatment regimen for pain relief takes into account the type of pain, available therapeutic modalities (nonpharmacologic and pharmacologic choices), and patient-specific risk factors for GI and cardiovascular events. Based on the current available evidence, it seems prudent that to minimize cardiovascular risk from coxibs, patients who have active atherosclerotic processes or recent cardiovascular events (such as bypass surgery, unstable angina, or acute myocardial infarction) or ischemic cerebrovascular events should avoid coxib use if possible.<sup>58</sup> If coxibs are indicated, the smallest effective dose for the shortest duration should be used. Traditional NSAIDs also carry cardiovascular risk, however, and similar to coxibs, these vary with individual agents. Although most guidelines suggest that naproxen may carry the least risk for major thrombotic events, the data to support these recommendations are scarce. Moreover, for patients taking an

aspirin for cardiovascular protection, data suggest that ibuprofen may interfere with aspirin's antiplatelet actions, theoretically undermining its protective effects, although this has not been proved.<sup>60</sup> Additionally, the use of aspirin likely negates the GI protective effects of a coxib. Treatment considerations for analgesics include careful assessment of GI and cardiovascular risk, individual pain relief needs, and use of potential concomitant therapies for GI and cardiovascular protection.

### SUMMARY

Coxibs have become an important part of the armamentarium of clinicians treating patients who have arthritis. Although celecoxib remains the only coxib available in the United States currently, other agents are available outside the United States and may undergo FDA review in the near future. Although the data strongly support increased risk associated with multiple cox-2 inhibitors, the risk seems to be dose and possibly dosing interval dependent. Moreover, that risk may vary enough by a patient's individual baseline cardiovascular risk that these factors should be considered when prescribing coxibs to individual patients. Although the current AHA recommendations suggest naproxen as the best NSAID alternative to coxibs, it is not entirely clear that traditional NSAIDs, which are available over-the-counter, such as naproxen or even ibuprofen, are risk-free.

In summary, multiple COX-2 selective inhibitors have been associated with increased cardiovascular risk in randomized, placebo-controlled trials. It is difficult not to consider this a class effect, although there may be real differences in the degree of risk between drugs. The data strongly suggest a dose response and that there may be real differences between dosing regimens and dosing intervals. Prescribers of cox-2 inhibitors should thus use the lowest possible dose, and as with all drugs, potential risks must be weighed against potential benefits.

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