

Cardiovascular Effects of Selective COX-2 Inhibition: Is There a Class Effect? The International COX-2 Study Group

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ABSTRACT. The International COX-2 Study Group, a panel of independent physicians and scientists, convened January 28-30, 2005, in Washington, DC, to discuss the issues concerning the cardiovascular (CV) profile of coxibs. The purpose of the meeting was to review potential mechanisms by which inhibition of COX-2 by selective and nonselective NSAID could increase risk of CV events, to evaluate the similarities and differences between drugs based on mechanism and pharmacology, and to propose potential trial methodology to more definitively answer questions regarding cardiovascular risk. (First Release May 15 2006; J Rheumatol 2006;33:1403-8)

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Introduction

The International COX-2 Study Group, a panel of independent physicians and scientists, convened January 28-30, 2005,

in Washington, DC, to discuss the issues concerning the cardiovascular (CV) profile of coxibs.

Increasing awareness of gastrointestinal (GI) toxicity produced by conventional, nonselective nonsteroidal antiinflammatory drugs (NSAID) led to the development of targeted inhibition of inflammation and pain with the discovery of the cyclooxygenase-2 (COX-2) enzyme. Drugs that selectively inhibit COX-2 activity were developed to treat pain and inflammation while hopefully sparing the GI tract. However reassuring the endoscopy trial results, the medical community required proof that these drugs were different from the nonselective NSAID. Thus, large scientific studies such as the Celecoxib Long-term Arthritis Safety Study (CLASS), Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, and Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) were designed to address these issues.

The first evidence of increased CV risk associated with selective COX-2 inhibition emerged from the VIGOR trial, in which a demonstrated 5-fold increased incidence of nonfatal myocardial infarction (MI) was observed in rofecoxib-treated individuals, compared with those receiving naproxen¹. Critics suggest that VIGOR demonstrated the CV risk of rofecoxib, while others highlight the previous safety record of rofecoxib in placebo-controlled and in epidemiologic studies comparing it with other non-naproxen NSAID. Possible explanations for these observed effects included rofecoxib-induced increased risk of cardiovascular events, cardioprotection by naproxen, a combination of the 2, or simply bad luck. By contrast, CLASS² failed to show a difference in CV risk with celecoxib, compared with either diclofenac or ibuprofen. No true placebo arm could be studied since the recruited patients had arthritis.

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After VIGOR, 2 important pharmacoepidemiologic studies yielded conflicting data on CV risk. Ray, *et al* reported that rofecoxib at doses > 25 mg/day increased risk of CV events in the first 90 days of exposure³, while Mamdani, *et al* reported no increase in CV adverse events with rofecoxib and no decrease with naproxen⁴.

In 2004, the Adenomatous Polyp Prevention on Vioxx (APPROVe) study had a confirmed thrombotic secondary outcome endpoint, and resulted in the voluntary withdrawal of the rofecoxib⁵.

As conventional NSAID also inhibit COX-2, questions also arose about the safety of these drugs, in that CLASS and TARGET revealed that there were no differences between celecoxib, ibuprofen, and diclofenac and lumiracoxib, naproxen, and ibuprofen, respectively. The Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), a 3-year multicenter study that randomized 2400 participants to 200-mg twice-daily celecoxib, 220-mg twice-daily naproxen, or placebo, was halted when naproxen appeared in a preliminary review of the accumulating results to increase the risk of CV events⁶. The celecoxib arm was also suspended when there was an observed dose-response for risk of CV events [stroke, MI, sudden cardiac death, and congestive heart failure (CHF)] in patients participating in the Adenoma Prevention with Celecoxib (APC) Study⁷. The exact mechanism by which these drugs may elevate CV risk remains unclear.

Roughly 6 weeks after a US Food and Drug Administration (FDA) joint advisory panel, held February 16–18, 2005, the agency took sweeping action in regard to the NSAID. Valdecoxib (Bextra®) was voluntarily withdrawn, due to increased risk of serious skin reactions along with a data-set with limited safety data concerning either GI or CV risk. In addition, there were prospective studies delineating increased CV risk in patients undergoing coronary artery bypass surgery and treated with the intravenous form of valdecoxib (paracoxib). The FDA also called for “black box” warnings regarding CV risk on all prescription NSAID, that is, all drugs that inhibit COX-2 activity whether selective or not. In addition, more specific labeling on over-the-counter (OTC) NSAID to reflect these potential risks was required. All prescribed NSAID also will be required to include a medication guide to advise patients of the risk for CV and GI events. The FDA also requested that OTC NSAID add a warning about potential skin reactions.

The purpose of this meeting was to review potential mechanisms by which inhibition of COX-2 by selective and non-selective NSAID could increase risk of CV events, to evaluate the similarities and differences between drugs based on mechanism and pharmacology, and to propose potential trial methodology to more definitively answer questions regarding cardiovascular risk.

The Cardiovascular Biology of the Coxibs

Unlike aspirin and nonselective NSAID, COX-2 inhibitors depress systemic prostaglandin I₂ (PGI₂) without concomitant

inhibition of platelet-derived thromboxane (TXA₂). This may result in an augmented response to thrombotic and hypertensive stimuli and could explain the observed acceleration of atherogenesis in mice. Even before their introduction in 1999, evidence had emerged that COX-2 inhibitors decreased PGI₂ production and would affect the balance between prothrombotic and antithrombotic eicosanoids. This raised the prospect that by decreasing vasodilatory and antiaggregatory PGI₂ production, selective COX-2 inhibitors might tip the balance in favor of prothrombotic eicosanoids (i.e., TXA₂) and might lead to increased CV events.

This concern was amplified by the increased risk of MI observed in patients receiving rofecoxib in the VIGOR trial¹, which demonstrated a clear reduction in adverse GI events, but an increased incidence of nonfatal MI in rofecoxib-treated individuals, compared with those receiving naproxen. In addition, results from the APPROVe study also provided clear evidence of an increase in CV risk in a manner consistent with this mechanistic explanation⁵.

Given the biological plausibility of, and the emergence of evidence for, an increase of MI and stroke in placebo-controlled trials of 3 structurally distinct COX-2 inhibitors, a class effect was suggested. However, manifestations of hazard at an individual level would be expected relative to the selectivity for COX-2 inhibition attained *in vivo*, dose, duration of exposure, and factors that influence interpersonal differences in drug response.

Manifestation of hazard does not only relate to a “balance” between TXA₂ and PGI₂. Thus, PGI₂ would be expected to act as a constraint on any stimulus to platelet activation, atherogenesis, or elevation in blood pressure. Therefore aspirin would be expected to ameliorate, but not eliminate, a hazard from COX-2 inhibitors.

Low-Dose Aspirin, Coxibs, and Cardiovascular Disease: Is COX-Isoenzyme Selectivity the Key?

If the vascular consequences of endothelial COX-2 inhibition are modulated only by profound and persistent blockade of platelet COX-1 activity, then the CV effects of most conventional NSAID may resemble those of selective COX-2 inhibitors. There is no evidence for its dependence on variable COX-2 selectivity; therefore, most conventional NSAID are likely to carry the same CV risk as coxibs, when used at comparable COX-2-inhibiting doses.

Unfortunately, NSAID have been investigated inadequately with regard to their CV effects, despite being widely prescribed. In fact, the largest trial of diclofenac comprised just 473 patients with osteoarthritis (OA) and extraarticular rheumatism⁸. Aspirin virtually and completely suppresses thromboxane (TXA₂) production throughout dosing intervals, while conventional NSAID do not do so persistently. Selectivity for COX-2 over COX-1 inhibition varies greatly between different drugs. For example, celecoxib is only modestly COX-2-selective compared with rofecoxib. Diclofenac,

nimesulide, and meloxicam exhibit modest COX-2 selectivity as well⁹. The selectivity of ibuprofen and other conventional NSAID is not known.

When the biosynthesis of TXA₂ is persistently enhanced, there is an association with major CV risk. It is only episodically enhanced in acute coronary syndrome and acute ischemic stroke. Thus, the role of TXA₂ in vascular occlusion appears hierarchically different in coronary versus cerebrovascular districts. Virtually complete and persistent blockade of platelet COX-1 is required to decrease the risk of TXA₂-mediated vascular occlusion. The effect of inhibiting PGI₂ production on TXA₂-mediated vascular occlusion in the face of complete and persistent blockade of COX-1 is not fully known.

Inhibiting a COX-2 product such as PGI₂ appears to enhance the risk of developing a nonfatal MI, a vascular event in which the platelet synthesis of TXA₂ has an important role, as reflected by the efficacy of low-dose aspirin. Aspirin inhibits platelet function by permanently blocking the COX-1 channel. This results in a dose-dependent inhibition of COX-1 activity, as reflected by TXA₂ production *ex vivo*, and explains aspirin's effect on reducing risk of MI among high-risk individuals. The administration of low-dose aspirin over 5 weeks can decrease vascular mortality by as much as 25%.

This enhanced coronary risk is probably related to the extent (as a function of dose) and persistence (as a function of pharmacokinetics) and dosing regimen of COX-2 inhibitor. The effect of treatment duration is not clearly established.

The Role of Pharmacokinetics in the Development of Cardiovascular Side Effects of Coxibs

Possible overlapping mechanisms that may help explain the CV effects of coxibs include increased blood pressure, inhibition of renal function¹⁰, and reduced production of vasculo-protective prostacyclin in the arterial endothelium, as well as alteration of the prostacyclin/TXA₂ balance. Obviously, the production of COX-2-dependent prostacyclin in endothelial cells will depend on pharmacokinetics — the presence and concentration of selective or nonselective inhibitors in the blood.

Understanding the pharmacokinetic differences among these drugs may help to maximize their effectiveness and minimize their CV risk. Indeed, we have shown recently¹¹ that measuring COX-2-dependent eicosanoid production *ex vivo* may help us to predict the longterm CV risk of a particular drug administered on a given dosing schedule.

These differences may also depend on preexisting CV risks; these should be determined before starting treatment by objective means such as measurement of the N-terminal portion of pro-brain natriuretic peptide (NT-pro-BNP), a general marker of CV risk conditions¹².

All inhibitors of cyclooxygenase are not without risk in longterm use. Their prolonged presence throughout the body corresponds with high efficacy, but also with increased risk —

at least in some patients. Fast elimination, intermittent use, and tissue selectivity, however, appear to decrease risk. FitzGerald and Patrono¹³ note that the clinically important pharmacokinetic differences between celecoxib and rofecoxib are related to oral bioavailability, half-life, and hepatic metabolism. This finding is further detailed in Brune and Hinz¹⁴.

Although the currently available coxibs differ in terms of absorption, distribution, and elimination, current dosing regimens do not take these differences into account. Drugs with a small volume of distribution and a short half-life exert fewer effects on the CV system than drugs characterized by homogeneous distribution throughout the body and prolonged presence in the bloodstream. Thus, drugs with a short half-life taken once daily might be less likely to increase CV risk. For drugs with slow elimination, intermittent use may be best to allow for a recovery phase. If the half-life is 2 days, for example, a week-long therapeutic pause is advisable.

Cardiovascular Effects of Coxibs: Facts and Myths

In December 2004, the results of the Adenoma Prevention with Celecoxib study⁷ demonstrated a dose-related increase in the risk of a composite of CV events (CV death, nonfatal MI, stroke, and CHF) among patients randomized to celecoxib versus placebo. Another prospective prevention study of celecoxib, the Prevention of Spontaneous Adenomatous Polyps Trial (PreSAP)¹⁵, however, did not show an increased CV risk associated with celecoxib compared with placebo.

Results from large epidemiologic studies suggest that celecoxib may be less hazardous than rofecoxib¹⁶, etoricoxib^{17,18}, or valdecoxib¹⁹. This may reflect differences that may include chemical structure (celecoxib is a sulfonamide, rofecoxib, a sulfone), pharmacokinetic properties, and subsequent metabolism. Intriguingly, the sulfone COX-2 inhibitors rofecoxib and etoricoxib might increase blood pressure to a greater extent than celecoxib and NSAID^{15,20}.

While COX-2-selective inhibitors invariably cause an imbalance between prostacyclin and TXA, multiple and opposing CV influences may be operating. If the prostacyclin/TXA₂ theory held true, one would have expected COX-2 drugs to exert consistent detrimental effects on endothelial function. However, celecoxib improved endothelium-dependent vasodilation in studies in patients with ischemic heart disease or hypertension (HTN)^{21,22}. An increasing body of evidence suggests that the putative harmful effects of celecoxib on prostacyclin may be counterbalanced by its beneficial effects on inflammation, oxidation, and the L-arginine/nitric oxide and Jun N-terminal kinase pathways. Because nitric oxide is a potent endothelial vasodilator that also reduces leukocyte proliferation, migration, adhesion, and vascular inflammation, these pathways are as important as prostacyclin and must be added to the equation to truly understand the effect a coxib will have on vessel-wall function.

Importantly, if the prostacyclin/TXA imbalance theory represented the only mechanism to explain the observed CV safe-

ty effect, adding aspirin should eliminate the risk. However, in the coxib trials, particularly in the CABG study with valdecoxib, patients also received aspirin and clopidogrel, and these COX-1 inhibitors did not prevent CV effects²³. The interim analysis of the placebo-controlled Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), comparing naproxen 220 bid versus celecoxib 200 bid, showed a notable trend toward increased events associated with the use of naproxen compared with celecoxib⁶. Similarly, several recently published case-controlled analyses also raised the possibility of CV toxicity for traditional NSAID. This is particularly cogent, as many patients are being switched back from the coxibs to these agents on the presumption of greater CV safety; however, no randomized trial has been performed to specifically evaluate this presumed benefit.

The TARGET Trial

TARGET was designed to answer several questions unanswered by the CLASS and VIGOR trials. Such questions include whether COX-2 inhibitors reduce ulcer complications and what the effects of low-dose aspirin might be. VIGOR revealed an improved GI outcome with rofecoxib, while CLASS failed to show a reduction in GI complications. TARGET utilized a larger sample size and also enrolled patients taking low-dose aspirin²⁴. Of the more than 18,000 patients with osteoarthritis (OA) who were enrolled, 3000 were "high-risk" from a CV perspective based on the HOPE trial criteria (high Framingham score or a history of vascular disease including MI and stroke, or diabetic patients with at least one risk factor), and 24% were taking low-dose aspirin. TARGET was a double-blind, randomized, active-controlled, 2-parallel subgroup, 12-month study evaluating lumiracoxib 400 mg once daily (2 to 4 times the recommended dose for OA), compared with naproxen (500 bid) and ibuprofen (800 tid).

About 9000 patients were randomized to the lumiracoxib arm, about 4700 to naproxen, and about 4400 to ibuprofen. Patients were followed regularly up to Week 52, with multiple visits at 4- to 8-week intervals²⁴. About 60% of the patients received all 52 weeks of therapy.

TARGET results showed that there was a nonsignificant trend for a 1.4 relative risk of CV events in the lumiracoxib group compared with naproxen, and those patients assigned to ibuprofen had similar results²⁴.

Risk of ulcer complications was reduced by 79% among patients given lumiracoxib compared with patients taking the other NSAID, although this benefit was not observed in patients taking aspirin²⁵. Of the roughly 9000 patients prescribed lumiracoxib, 6 cases of jaundice were observed (0.07%). There were 2 cases of jaundice in the group taking ibuprofen (0.05%), and one case among those taking naproxen (0.02%). All adverse events resolved fully after discontinuation of therapy.

Schnitzer, *et al*²⁵ report that lumiracoxib showed a 3- to 4-

fold reduction in ulcer complications compared with NSAID, with no increase in the rate of serious CV events. In patients not taking aspirin, the cumulative one-year incidence of ulcer complications was 1.09% with NSAID (64 events) versus 0.25% with lumiracoxib (14 events). Reductions in ulcer complications were also significant in the overall study population, but not in those taking aspirin, while 0.55% of those taking NSAID and 0.65% of those taking lumiracoxib reached the CV endpoint.

COX Inhibition, Hypertension, and Edema Effect (Ambulatory BP)

Even if they are mechanistically different, COX-2 inhibitors have effects on HTN similar to those observed with conventional NSAID. Pope, *et al* demonstrated that use of nonselective NSAID in treated hypertensive patients, including those taking angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, results in an average unadjusted increase in mean arterial pressure ranging from 0.61 mm Hg with aspirin to 6.10 mm Hg with naproxen²⁶. This is a common problem in the OA population. Singh, *et al* report that 40% of the 24.3 million people in the US with OA have HTN²⁷.

All coxibs induce salt and water retention and destabilization of blood pressure (BP), as do conventional NSAID. Additionally, there is a dose-related effect with rofecoxib at doses between 12.5 mg and 50 mg (with a markedly increased percentage of patients with BP elevation at the 50 mg dose). There are also dose-related increases with valdecoxib at 40 mg and 80 mg. Bensen, *et al*²⁸ report that 2.7% of patients with rheumatoid arthritis (RA) taking valdecoxib 40 mg/day develop HTN.

In the Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial (CRESCENT)²⁹, rofecoxib significantly increased 24-hour BP during and at landmarks after 6 weeks of therapy, while celecoxib and naproxen did not, as determined by ambulatory BP measurements. In CRESCENT, patients using rofecoxib, but not celecoxib or naproxen, had an increased rate of edema (23.3% vs 18.0%), while the rates for celecoxib and conventional NSAID were 17.5% and 18.2%, respectively.

The CLASS², VIGOR¹, and TARGET²⁴ trials all suggest that COX-2 inhibitors can increase BP. In CLASS, there was a relatively low, non-dose-dependent incidence of HTN with celecoxib when compared with diclofenac and ibuprofen².

In a 6-week, randomized, double-blind study of edema and HTN during treatment with rofecoxib 25 mg daily and celecoxib 200 mg daily in OA patients with HTN, Whelton, *et al*³⁰ found that edema and BP destabilization (systolic pressure increase) were more common in patients receiving rofecoxib than in those receiving celecoxib.

NSAID use is not associated with incident CHF; however, once CHF is present, there is a substantial increase in risk with NSAID use, according to Feenstra, *et al*³¹.

Nevertheless, compared with HTN, there are markedly

fewer data with regard to CHF and edema. In one study by Mamdani, *et al*³², patients taking rofecoxib and nonselective NSAID (but not celecoxib) had an increased risk of hospital admission for CHF, relative to non-NSAID users. In TARGET, CHF occurred with similar frequency among lumiracoxib users (0.24%) and NSAID users (0.34%)²⁴.

Renal Effects of COX Inhibition

Until recently, COX-1 had been considered the physiologically important isoform responsible for prostaglandin synthesis in the normal kidney. Researchers therefore initially postulated that selective COX-2 inhibitors would be free of adverse renal effects. However, accumulating evidence suggests that this is not the case, and it is thought that the renal effects of COX inhibition may contribute to the increased CV risk seen with coxibs.

An analysis of a Medicare database from 1994³³ showed that patients prescribed an NSAID had an increased risk of subsequently requiring a prescription for an antihypertensive agent, regardless of which nonselective NSAID they were taking. NSAID predispose to HTN by interfering with the normal effects of prostaglandins that prevent its development. Prostaglandins are vasodilators that oppose the effects of constrictors such as angiotensin and vasopressin, and promote dilation of resistance vessels. In addition, prostaglandins promote the kidney's ability to excrete salt and water. When an NSAID blocks these functions, there is accentuated pressor activity as well as increased sodium and water retention (both of which promote HTN).

In a series of mouse studies, Qi, *et al*³⁴ infused angiotensin II to see whether COX-1 or COX-2 was the relevant isoenzyme that normally buffered its pressor effects. The infusion of a moderate dose of angiotensin II led to about a 10% increase in mean arterial pressure over about 30 minutes. This tended to drift down over a 45-minute period, but remained above baseline. Pretreatment with a COX-2 inhibitor markedly increased the pressor effects of angiotensin II. This suggests that COX-2 normally produces a vasodilator and that, when the synthesis of this vasodilator prostaglandin is blocked, its vasodilator effect is abolished, revealing the full pressor effects of angiotensin II. In contrast, selective inhibition of the COX-1 isoform had the opposite effect.

Similarly, the effects on urinary salt excretion differ between the 2 isoenzymes. Reduced renal medullary blood flow occurs following COX-2 inhibition, providing direct evidence that the agent promotes vasodilation of the medullary vasculature. COX-1 inhibition does not produce such effects. Further, COX-2 inhibition blunts urinary sodium excretion, while COX-1 inhibition may enhance it. The loss of these natriuretic endogenous COX-2-derived prostaglandins that results when their synthesis is blocked by the action of an NSAID probably contributes to sodium retention in patients taking NSAID and coxibs.

A significant percentage of people receiving coxibs devel-

op edema associated with reduced renal salt excretion. The main intrarenal source of the endogenous natriuretic prostaglandins that would normally prevent this effect appears to be renal medullary interstitial cells. Both COX-1 and COX-2 are especially abundant in the renal medulla, with COX-1 primarily expressed within the collecting duct and COX-2 mainly restricted to the interstitial cells. A recent study by Zewde and Mattson³⁵ found that sustained intramedullary infusion of a COX-2 inhibitor caused a prompt and dramatic increase in BP, whereas intravenous infusion of the COX-2 inhibitor caused only a comparatively mild increase in BP. The hypertensive effects of intramedullary COX-2 inhibition also depend on dietary salt and suggest a particularly important role for medullary interstitial cell COX-2 products and their natriuretic effects.

Conclusions

The widespread use of coxibs and NSAID, coupled with the prevalence of risk factors for adverse CV events in the treated populations, makes understanding of the benefits and risks of these agents essential. In the rush to perform large studies to meet regulatory and labeling requirements, certain basic mechanistic studies for coxibs have not been performed. The situation is even more dismal for nonselective agents, for which large prospective studies have never been performed. Although conference attendees were particularly enthusiastic about the prospect of mechanistic and classical pharmacologic studies of the drugs, participants endorsed the need for studies specifically designed to address clinical CV risk. Only when both risk and benefit are more clearly understood will clinicians be prepared to determine with their patients when use of these drugs is appropriate.

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