

Cardiovascular Effects of the Cyclooxygenase Inhibitors

William B. White

Cyclooxygenase (COX)-2 selective inhibitors were developed to create a new class of nonsteroidal anti-inflammatory drugs (NSAIDs) with properties similar to those of nonselective NSAIDs but without their potential COX-1-mediated gastrointestinal toxicities.^{1,2} Studies of the various COX-2 selective inhibitors have shown that they are in fact associated with a significantly lower risk of upper and lower gastrointestinal complications than traditional NSAIDs, except in patients who are taking concomitant low-doses of aspirin.

Recent evidence also suggests that some doses of the COX-2 selective inhibitors, and perhaps some traditional NSAIDs as well, are associated with an increased risk of adverse cardiovascular (CV) events. Reports of a higher incidence of myocardial infarction (MI) among patients with arthritis taking high doses of the COX-2 selective inhibitor rofecoxib compared with those taking the NSAID naproxen²⁻⁴ have had heightened concerns since 2001 regarding selective COX-2 inhibitor safety. In addition, in early 2005, elevated CV event rates were reported in patients with spontaneous adenomatous polyps who were taking high doses of celecoxib compared with placebo⁵ and in patients who received parenteral parecoxib followed by oral valdecoxib versus placebo immediately after coronary artery bypass graft surgery.⁶

This article represents a compilation of the data concerning the effects of both nonselective and selective NSAIDs on blood pressure (BP), particularly in patients with hypertension and/or on antihypertensive agents. Subsequently, the impact that the COX inhibitors have on CV events from several recent clinical trials for the treatment of arthritis or for cancer prevention, as well as from selected large observational studies, is discussed.

CV Pharmacology of COX Inhibition

COXs participate in numerous physiological functions and human pathological disorders. The COX-1 isoform is constitutively expressed in most tissues where it regulates the synthesis of prostaglandins. COX-1 is the only form of the enzyme in mature platelets and is also expressed in the vascular endothelium, the gastrointestinal epithelium, brain, spinal cord, and kidney. The COX-2 isoform plays an important role in induction of inflammation in response to injury, as well as

later repair of inflammation. It is noteworthy that COX-2 may be induced by bacterial endotoxins, cytokines, and growth factors and is expressed in atherosclerotic plaques, during angiogenesis, during wound healing, and in a variety of epithelial cell cancers.⁷⁻⁹ In addition, COX-2 is constitutively expressed in the macula densa and renal medullary interstitium.^{10,11} As discussed below, one result of COX-2 inhibition is a reduction in natriuresis and the development of hypertension in susceptible populations. The COX isoenzymes are similar in structure, but the substrate-binding channel of COX-2 contains a side pocket that is absent in COX-1. This structural difference has allowed for the design and development of COX inhibitors with side chains that fit within the COX-2 channel but are too large to block COX-1 with equivalent affinity. As a result, it has been common to determine the "selectivity" of a compound by its ratio of affinities to COX-1 and COX-2. This selectivity can be influenced by pharmacokinetics and pharmacodynamics of both the nonselective NSAIDs, as well as the specifically developed COX-2 selective inhibitors.¹²

The nonselective and selective (COX-2) NSAIDs are a diverse group of compounds that are unified by their inhibition of prostaglandin (PG) biosynthesis. Inhibition of COX alters the metabolism of eicosanoids, including PGs, thromboxane, and leukotrienes, which are derived from arachidonic acid. Cyclooxygenase is the rate-limiting enzyme for the conversion of arachidonic acid to the labile intermediate PGH₂, which is then converted to the eicosanoids thromboxane A₂ and prostacyclin by thromboxane synthase and prostacyclin synthase, respectively. PGH₂ also serves as a substrate for other PGs, such as PGE₂ and PGD₂, that are formed by specific isomerases.¹² However, among the members of the class of these agents, there are substantial variations in chemical structure, COX-2 selectivity, and pharmacokinetics (Table 1).

The basic literature is replete with recent studies demonstrating that genomic or pharmacological removal of prostacyclin leads to both platelet-dependent¹³⁻¹⁵ and platelet-independent¹⁶ mechanisms for induction of thrombosis, plaque destabilization, or atherogenesis. In addition, COX-2 is recognized as a key source of prostacyclin under normal laminar flow conditions in the vasculature and has been shown to be cardioprotective in ischemia-reperfusion injury.¹⁷

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TABLE 1. The NSAIDs and COX-2 Selective Inhibitors

Chemical Name	Common Brand Names	Chemical Group	Half-Life, h
Nonselective NSAIDs			
Diclofenac	Cataflam, Voltaren, Arthrotec	Heteroaryl acetic acid	4 to 6
Diflunisal	Dolobid	Nonacetylated salicylate	8 to 12
Etodolac	Lodine, Lodine XL	Indole acetic acid	3 to 7
Fenoprofen	Nalfon, Nalfon 200	Arylpropionic acid	3
Flurbiprofen	Ansaid	Arylpropionic acid	6
Ibuprofen	Motrin, Advil	Arylpropionic acid	2 to 3
Indomethacin	Indocin, Indocin SR	Indolic acid	4 to 5
Ketoprofen	Oruvail, Orudis	Arylpropionic acid	2 to 4
Ketorolac	Toradol	Heteroaryl acetic acid	4 to 7
Mefenamic acid	Ponstel	Fenamate	2
Meloxicam	Mobic	Enolic acid	12 to 14
Nabumetone	Relafen	Alkanones	24
Naproxen	Aleve, Naprosyn, Anaprox	Arylpropionic acid	13
Oxaprozin	Daypro	Arylpropionic acid	24
Piroxicam	Feldene	Enolic acid	40 to 50
Salsalate	Disalcid	Nonacetylated salicylate	16
Sulindac	Clinoril	Indole acetic acid	8
Tolmetin	Tolectin	Indole acetic acid	2 to 5
COX-2 selective NSAIDs*			
Celecoxib	Celebrex	Diarylheterocyclic sulfonamide	10 to 12
Etoricoxib	Arcoxia	Diarylheterocyclic sulfone	22
Lumiracoxib	Prexige	Diarylheterocyclic acetic acid	4
Parecoxib	Dynastat	Diarylheterocyclic (prodrug)	7
Rofecoxib	Vioxx	Diarylheterocyclic sulfone	17 to 18
Valdecoxib	Bextra	Diarylheterocyclic sulfonamide	10 to 14

*COX-2 selective inhibitors are defined based on their lack of platelet inhibition at supratherapeutic doses rather than by in vitro selectivity.

Thus, some investigators hypothesize that COX-2 inhibition in vascular inflammatory states would lead to a decrease in antithrombotic prostacyclin made by arachidonate flux and would provide enhanced leukotriene synthesis along with increased reactive oxygen species and consumption of anti-thrombotic NO.¹⁸ In contrast, other reports have demonstrated that COX-2 inhibition improves the vascular endothelial dysfunction that is mediated through reduced NO availability and oxidative stress.¹⁹ In addition, a recent study showed that selective COX-2 inhibition led to reduced tissue factor expression and activity in human endothelial cells that was mediated by inhibition of c-Jun terminal NH₂ kinase phosphorylation.²⁰ In these 2 latter studies, the authors suggested that heterogeneity of responses of various inhibitors of COX-2 might lead to different clinical effects, especially in patients with underlying atherosclerotic vascular diseases. Thus, mechanistic gaps in our understanding of COX inhibitors related to vascular pathophysiology are apparent.

Effects of COX Inhibitors on the Gastrointestinal Tract

The development of the selective COX-2 inhibitors was based on concerns associated with the effects of COX-1 inhibition on the upper gastrointestinal tract. The gastrointes-

tinal adverse effects of aspirin and traditional NSAIDs are well defined and include development of gastric or duodenal ulcers, hospitalizations because of gastrointestinal bleeding complications, perforated ulcers or gastric obstruction, and gastrointestinal-related deaths.^{21,22} Lower rates of these complications during the past decade have been attributed to the use of lower nonselective NSAID doses, concomitant use of proton pump inhibitors, and the introduction of COX-2 selective inhibitors, which are fundamentally COX-1-sparing drugs.²³

The gastrointestinal toxicity of traditional NSAIDs is attributable in part to nonselective inhibition of both COX-1 and COX-2 isoenzymes involved in PG synthesis.²⁴ Data from large-scale clinical trials have confirmed that COX-2 inhibitors are associated with substantial reductions in gastrointestinal risk in the majority of patients who do not use aspirin. Clinical trials demonstrate that COX-2 inhibitors are associated with a reduction in risk of gastrointestinal adverse events, including endoscopic ulcers, equivalent to that achieved by adding proton pump inhibitor therapy to traditional NSAID therapy.^{25,26} Regardless of the dose of the COX-2 selective inhibitor, endoscopic findings for these agents are not significantly different from those observed for placebo.²⁶

The Vloxx Gastrointestinal Outcomes Research (VIGOR)² Study was the first large-scale trial to provide evidence that COX-2 selective inhibitors minimize the risk of upper gastrointestinal adverse effects in older (age ≥ 50 years) patients with rheumatoid arthritis.² Over 9 months of follow-up, rofecoxib 50 mg once daily and naproxen 500 mg twice daily showed equivalent efficacy; however, the incidence of confirmed upper gastrointestinal adverse events per 100 patient-years in the rofecoxib group was less than half of that observed in the naproxen group. Of interest, a posthoc analysis of the trial indicated that $\approx 40\%$ of the serious events occurred in the lower gastrointestinal tract; these events were also reduced by more than half in patients who received rofecoxib.²⁷ It has been of concern that there is no evidence that proton pump inhibitors decrease the incidence of lower gastrointestinal tract complications in patients receiving NSAIDs.

The CeLecoxib Arthritis Safety Study (CLASS) provided additional evidence that COX-2 inhibitors reduce the risk of gastrointestinal events in adults with osteoarthritis or rheumatoid arthritis.¹ Patients enrolled in CLASS were randomly assigned to receive celecoxib 400 mg twice daily versus ibuprofen 800 mg thrice daily or versus diclofenac 75 mg twice daily and were permitted to take low-dose aspirin (≤ 325 mg daily) if indicated for CV prophylaxis. During the 6-month treatment period, the annualized incidence of upper gastrointestinal complications alone and in combination with symptomatic ulcers was nearly twice as high among patients who received the nonselective NSAIDs as among those who received celecoxib. In addition to minimizing ulcers and their complications, studies typically show that the COX-2 inhibitors are better tolerated than traditional NSAIDs.²⁸ Of importance, however, is that the subgroup of patients who were taking chronic low-dose aspirin (21% of the patients at doses of 81 to 325 mg daily) failed to show a significant reduction in gastrointestinal complications for celecoxib relative to the nonselective NSAIDs in the CLASS trial. Similar findings have occurred with endoscopic and gastrointestinal outcome studies with the newer COX-2 inhibitors etoricoxib, lumiracoxib, and valdecoxib.^{29–32}

COX Inhibitors in Patients With Hypertension

Coadministration of NSAIDs or COX-2 selective inhibitors with antihypertensive agents is quite common.³³ Meta-analyses of the NSAIDs from the early 1990s showed that many agents within the class (eg, ibuprofen, indomethacin, and naproxen) could increase mean arterial pressure by as much as 5 to 6 mm Hg in hypertensive patients.^{34,35} As reported by Grover et al,³⁶ increases in BP by NSAIDs of this magnitude are of sufficient magnitude to be of clinical concern. Sustained BP elevations in the elderly are associated with increases in the risk of both ischemic and hemorrhagic stroke, congestive heart failure, and ischemic cardiac events.^{37–39} In the VALUE Study, differences of ≈ 4 mm Hg in systolic BP control in an older population of hypertensive patients randomly assigned to 2 treatment groups (valsartan or amlodipine) resulted in a clinically and statistically significant relative increase in cardiac events of $>40\%$ in the less

well-controlled group (valsartan recipients) during the first 6 months of the trial.³⁹ Thus, it has become of clinical relevance to study the effects of the NSAIDs and COX-2 selective inhibitors on BP destabilization in patients with both treated and untreated hypertension.³³

Pathophysiologic Effects of NSAIDs and COX-2 Inhibitors on BP

COX-2 inhibition results in a reduction of PG synthesis and is associated with both antinatriuretic and vasoconstrictor effects.^{40–43} In some cases, these effects have consequences on BP control and may be of particular relevance in patients with preexisting hypertension, edema, or congestive heart failure.

Inhibition of COX-2 is associated with reductions in both PGE₂ and prostacyclin.⁴⁴ Inhibition of PGE₂ may induce an acute relative reduction in daily urinary sodium excretion of $\geq 30\%$.^{43,44} Within a few days, the kidneys in patients with normal kidney function will tend to increase sodium excretion to compensate for the antinatriuretic effects of the COX-2 selective inhibitor or NSAID to maintain homeostasis of sodium balance.⁴⁴ This phenomenon occurs in the absence of a rise in BP or sustained increases in plasma volume.⁴⁴ In patients with chronic kidney disease, this homeostatic process is often impaired and, within 1 to 2 weeks of initiating NSAID therapy, a considerable amount of salt and water may accumulate. In such cases, both edema and hypertension commonly develop and, in more severe cases, congestive heart failure develops.^{43–47}

In addition to causing problems with salt and water balance, the NSAIDs and COX-2 selective inhibitors may impair the vasodilatory benefits of prostacyclin. Loss of this mechanism of vasodilation in the face of numerous vasoconstrictors (eg, angiotensin 2, norepinephrine, and endothelin) may potentially lead to increases in systemic vascular resistance and, subsequently, to increases in mean arterial pressure. Pharmacological experiments in animals attempting to elucidate the differences among NSAIDs on hypertension and edema have yielded diverse results. Qi et al⁴⁸ used a mouse model to assess the effects of COX-1 and COX-2 on the pressor effect of angiotensin-2 using pharmacological inhibition or gene knockout of the COX isoenzymes. Their data showed that COX-1 inhibition blunted the pressor effect of angiotensin-2, whereas COX-2 inhibitors reduced renal medullary blood flow and urine flow and enhanced the pressor effect of angiotensin-2. Hermann et al^{49,50} assessed rofecoxib, celecoxib, diclofenac, and placebo on BP, endothelial function, renal morphology, and protein excretion in salt-sensitive rats. Their studies demonstrated that celecoxib, a selective COX-2 inhibitor, but not rofecoxib (a more potent COX-2 inhibitor) or diclofenac (a mixed COX-1 and COX-2 inhibitor), reduced glomerular injury and proteinuria and improved systolic BP and endothelial function while reducing oxidative stress. A more recent consideration has been the effects of NSAIDs on aldosterone metabolism. Winner et al⁵¹ have demonstrated that several nonselective NSAIDs inhibit the glucuronidation of aldosterone by human kidney microsomes, which could lead to hypertension through enhanced plasma and tissue concentrations of aldosterone.⁵²

Effects of NSAIDs and COX-2 Inhibitors in Normotensive Patients

The effects of chronic NSAID and COX-2 selective inhibitor therapies on normotensive patients have not been extensively studied. In a small, 1-week clinical study in normal healthy volunteers, COX-2 inhibition was less pronounced after treatment with celecoxib and rofecoxib compared with the nonselective NSAID diclofenac.⁵³ In fact, diclofenac also increased BP to a greater extent in the normotensive subjects compared with the selective COX-2 inhibitors; no increases in BP were found after rofecoxib administration, but an ≈ 10 -mm Hg increase in systolic BP after diclofenac was observed. In addition, in a pooled analysis of the effects of older NSAIDs on BP, indomethacin induced a slight elevation in BP in normotensive persons.³⁴

In a fairly recent case-control analysis in a Medicare population, Solomon et al⁴⁷ studied the effects of NSAIDs and coxibs on the development of hypertension. The primary finding in this study was that new-onset hypertension developed in 21% of patients for whom celecoxib was prescribed, 23% of those for whom nonselective NSAIDs was prescribed, and 27% of those for whom rofecoxib was prescribed. Of note, the background rate of new hypertension developing in this elderly patient population not receiving NSAIDs was 22%.^{33,47} The increased rates of hypertension induced by rofecoxib was significantly higher than with celecoxib and the nonselective NSAIDs. In addition, the risk was higher if patients had a history of congestive heart failure or kidney or liver disease.

Effects of NSAIDs and COX-2 Inhibitors in Treated Hypertensive Patients

A major focus of clinical research associated with the NSAIDs has been the potential destabilization of BP in hypertensive patients who are receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, β -blockers, calcium antagonists, or diuretics. In one of our earlier placebo-controlled trials, ambulatory BP monitoring was used to assess the effect of high-dose celecoxib (200 mg BID) in 178 patients who were on chronic ACE inhibitor therapy.⁵⁴ This study demonstrated that celecoxib (400 mg total daily dose) was associated with a nonsignificant increase in 24-hour mean BP of 1.6/1.2 mm Hg. Evaluation of the BP curves did suggest a transient (1- to 2-hour) increase in systolic BP after dosing of celecoxib, which could be associated with peak inhibition of COX-2. In a smaller but similar trial, Izhar et al⁵⁵ studied the effects of celecoxib and diclofenac on ambulatory BP and glomerular filtration rates in a double-blind crossover study. Mean 24-hour systolic BP was significantly increased by diclofenac (+4.2 mm Hg) compared with celecoxib (+0.6 mm Hg), and glomerular filtration rate was significantly reduced by diclofenac but not by celecoxib. The authors felt that these differences were attributable in part to the once daily dosing of celecoxib versus the twice daily dosing of diclofenac.

Subsequently, a larger trial using the clinic systolic BP as the primary end point evaluated the effects of rofecoxib 25 mg per day and celecoxib 200 mg per day in 1092 patients on chronic, stable doses of antihypertensive therapies.⁴⁵ This

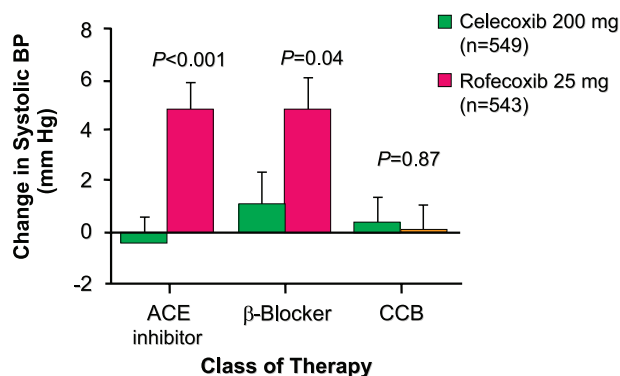


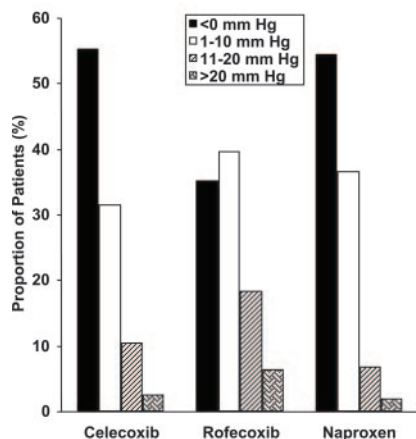
Figure 1. Effects of rofecoxib and celecoxib on clinic systolic BP in patients given ACE inhibitors, β -blockers, and calcium antagonists. Destabilization occurred after 6 weeks of treatment with rofecoxib in patients taking ACE inhibitors and β -blockers but not in those taking calcium antagonists. Celecoxib did not affect systolic BP control rates in the antihypertensive drug treatment groups. Reproduced by permission from Reference 45.

study showed that rofecoxib induced significant increases in systolic BP in patients who were taking ACE inhibitors and β -blockers but not in those who were taking calcium antagonists (Figure 1). These results support the notion that calcium antagonists do not significantly depend on vascular prostacyclin as part of their mechanism of action.^{40,56,57} Alternatively, calcium antagonists may not be influenced by increases in total body sodium as are the ACE inhibitors, diuretics, and blockers of the sympathetic nervous system. Our findings are supported by older studies with the NSAIDs. In a 3-week, placebo-controlled study by Houston et al,⁵⁶ neither ibuprofen nor naproxen significantly increased mean BP in patients treated with chronic verapamil therapy. Klassen et al⁵⁷ also showed this finding with nicardipine patients who were treated with naproxen.

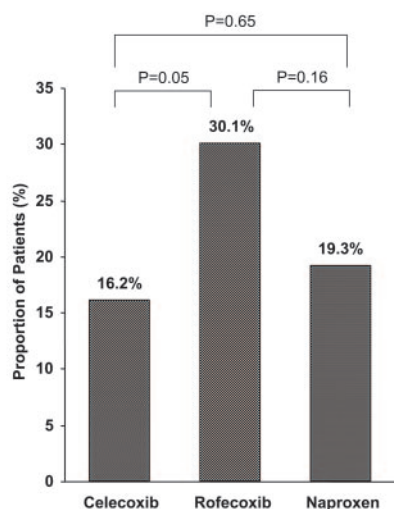
The Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial was a comprehensive randomized, double-blind clinical trial evaluating the effects of NSAIDs in treated hypertensive subjects on ACE inhibitors alone or in combination with other classes of antihypertensive therapy.²⁸ The primary end point was change from baseline in the 24-hour ambulatory systolic BP after 6 and 12 weeks of therapy with celecoxib, naproxen, or rofecoxib in ≈ 400 patients with type 2 diabetes, hypertension, and osteoarthritis. This study demonstrated that, at equally effective doses for osteoarthritis, treatment with rofecoxib 25 mg daily induced a significant destabilization of 24-hour systolic BP control compared with celecoxib 200 mg daily and naproxen 500 mg twice daily (Figure 2). As shown in Figure 2, 30% of patients administered rofecoxib had a resultant 24-hour systolic BP of ≥ 135 mm Hg compared with 16% of patients randomly assigned to celecoxib and 19% to naproxen. It is noteworthy that no baseline clinical characteristic was predictive of the development of hypertension on the NSAID or COX-2 selective inhibitor. During the course of the study, significantly more patients developed peripheral edema while taking rofecoxib compared with the other 2 treatment groups, but no patient developed kidney dysfunction.

Because NSAIDs and coxibs may have a destabilizing effect on BP within 1 to 2 weeks, they should be used with

Distribution of changes in ABPM systolic blood pressure at Week 6



Proportion of normotensive patients who became hypertensive at Week 6



Normotensive: Ambulatory Systolic Blood Pressure <math>< 135\text{ mm Hg}</math>
 Hypertensive: Ambulatory Systolic Blood Pressure $\geq 135\text{ mm Hg}</math>$

Figure 2. Effects of celecoxib, rofecoxib, and naproxen on changes in 24-hour mean systolic BP (left) and on proportion of patients who destabilized to hypertensive values (right) after 6 weeks of therapy. A consistent increase from baseline in ambulatory systolic pressure was observed only in the rofecoxib treatment group. Reproduced by permission from Reference 28.

caution in hypertensive patients who are taking ACE inhibitors, angiotensin receptor blockers, or β -blockers, as well as in patients who have diabetes or mild kidney disease. Of particular concern is that some patients are susceptible to the development of congestive heart failure. Data from population based cohort studies have demonstrated that patients who are prescribed NSAIDs and some COX-2 inhibitors develop substantially increased relative risks of hospitalization for heart failure compared with nonusers of NSAIDs.⁵⁸ Thus, hypertensive patients, especially those with a history of left ventricular hypertrophy and diastolic dysfunction, should be seen relatively soon (1 to 3 weeks) after anti-inflammatory therapy is initiated.

Evaluating CV Events in Clinical Trials of Arthritis With COX Inhibitors

CV event rates among users of NSAIDs, including COX-2 selective inhibitors, have been evaluated in numerous types of studies. The most robust data come from prospective, randomized clinical trials in which the double-blind was maintained for the entire course of the study. The seminal studies that first examined CV events in arthritis populations were the VIGOR² and CLASS studies.^{1,59} These 2 studies remain important with regard to outcomes, because they assessed suprathreshold doses of COX-2 selective inhibitors with maximal therapeutic NSAID doses in their target treatment population of osteoarthritis and rheumatoid arthritis. Findings were dissimilar for VIGOR and CLASS, as absolute (nonadjudicated) CV event rates were higher with rofecoxib 50 mg daily than with naproxen 500 mg twice daily in the VIGOR Trial,² whereas they were similar for celecoxib 800 mg daily, ibuprofen 2400 mg daily, and diclofenac 150 mg daily in CLASS (Figure 3).⁵⁹ The CV event rates in 2 meta-analyses of celecoxib and various NSAIDs^{60,61} in the osteoarthritis and rheumatoid arthritis populations confirmed that there were similar rates of Anti-Platelet Trialists' Collaboration (APTC)⁶² adjudicated end points.

Findings from a third outcomes study,⁶³ the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), assessed the investigational COX-2 selective inhibitor lumiracoxib (Figure 3). The cumulative incidence of adjudicated APTC events in TARGET was relatively low (<math>< 1\%</math>) but did not differ between lumiracoxib and naproxen or ibuprofen. There were no placebo or noninflammatory treatment arms in VIGOR, CLASS, or TARGET, because all of these patients suffered from arthritis and would not have tolerated a long-term trial without an active treatment.

The CV event rates in the arthritis trials range from 0.7% in the TARGET⁶³ treatment arms to $\approx 1\%$ in the CLASS treatment arms⁵⁹ and pooled analyses of clinical trials for celecoxib⁶¹ to $\approx 2\%$ in the rofecoxib arm in VIGOR.² Whereas the limitations of these trials include a lack of power required for elucidating CV risk in a definitive fashion and maximal treatment exposure of 15 months, the controlled clinical trial data do suggest that suprathreshold doses of celecoxib (800 mg daily) and lumiracoxib (400 mg daily) have CV risk that is similar to the nonselective NSAIDs.

The largest clinical trial evaluating a COX-2 selective inhibitor is the combined Multinational Etoricoxib and Diclofenac Arthritis Long-Term Trial with etoricoxib compared with the nonselective NSAID diclofenac.⁶⁴ With >43 000 patient-years of exposure, adjudicated APTC end points for etoricoxib (60 and 90 mg once daily) and diclofenac (75 mg twice daily) were similar. These results are also important, because some of the patient population was evaluated for 2 years.

Use of Parenteral COX-2 Inhibitors in the Perioperative Period

Parenteral administration of NSAIDs is used to reduce pain and lower opioid requirements after surgery. Parecoxib is the parenteral prodrug of the selective COX-2 inhibitor valdecoxib and is widely used outside of the United States for acute and perioperative pain.⁶⁵ A placebo-controlled randomized

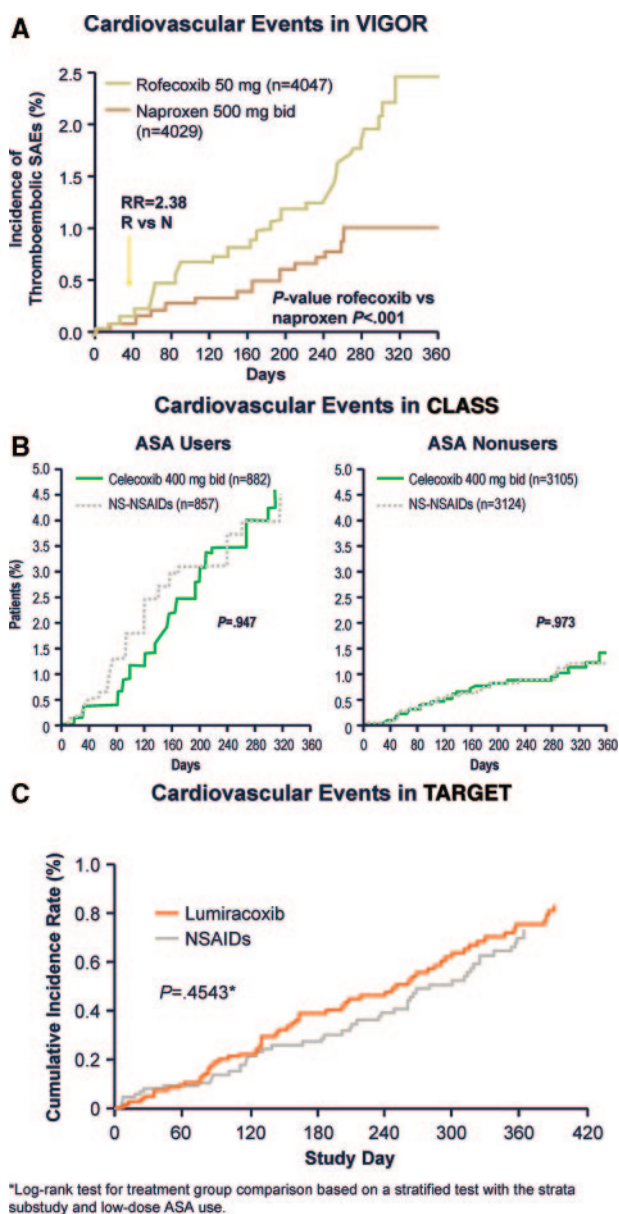


Figure 3. Accumulation of all CV events in the VIGOR Trial (A), the CLASS Trial, in which it was possible to analyze patient outcomes according to aspirin use (B), and the TARGET Trial (C). Cardiovascular events in TARGET were adjudicated as myocardial infarction, stroke, and cardiovascular death, whereas the events from VIGOR and CLASS are investigator reported and include any CV thrombotic event. Reproduced by permission from References 2, 32, and 59.

study of intravenous parecoxib sodium (3 days) followed by oral valdecoxib (7 days) in 1671 patients who had undergone coronary artery bypass graft surgery⁶ showed that patients receiving these agents had a postoperative CV event rate of 2% compared with a rate of 0.5% in patients receiving placebo. Of interest was the finding that 35% of the events in the active treatment group were observed in a 30-day period that followed discontinuation of the parecoxib and valdecoxib. The authors speculated that the coronary artery bypass graft patient group could be at particular risk for cardiac events because of preexisting generalized atherosclerotic disease along with the exposure to the additional thrombo-

genic risks of cardiopulmonary bypass and aortic cross-clamping.⁶ All of the patients in this trial were given low-dose aspirin, which should have mitigated against the formation of thromboxane A_2 , but aspirin resistance is known to occur after coronary artery bypass graft, and thrombocytosis occurs commonly 2 weeks after surgery.⁶⁶

The results of a large noncardiac surgery study was reported recently by Nussmeier et al⁶⁷ that used similar doses of parecoxib and valdecoxib and the same basic design. In this trial, 1062 patients participated after undergoing major orthopedic, abdominal, gynecologic, or noncardiac thoracic surgery. The rates for CV events were 1% in both the parecoxib and placebo groups. Patients in this study had less than a 10% history of cardiac disease, but more than one third had hypertension or other major cardiac risk factors. Thus, because these studies did demonstrate a substantial analgesic benefit with a reduction in opioid requirements, lower-risk patients undergoing surgery might be appropriate candidates for parecoxib, whereas patients undergoing cardiac surgery are not.

Observational Studies That Have Assessed the CV Risk of NSAIDs and COX-2 Selective Inhibitors

CV event rates have been evaluated in numerous databases from healthcare companies, insurance rosters, and pharmacy benefit management companies. It is not possible to review the scores of studies that have been published during the past 5 years evaluating the relative risk of MI and other CV events in patients exposed to NSAIDs. Thus, this discussion is limited to the largest and most prominent observational studies.^{68–71}

The observational studies are virtually all retrospective and used either nested case-control or cohort analyses based on drug use in the database. Therefore, they will always pose some methodologic concerns related to confounding, selection bias, and lack of information on nonprescription drugs, smoking status, and aspirin use. However, the magnitude of the populations studied and the hundreds to thousands of CV events analyzed do enhance their value from both clinical and epidemiological perspectives.

The largest observational cohort study was performed by the US Food and Drug Administration using a database of Kaiser Permanente in Northern California.⁶⁸ Using a case-control design, Graham et al⁶⁸ studied ≈ 1.4 million people, who were observed for 2 years. Nonusers (including those who were remote users) of NSAIDs served as control subjects, and nonfatal MI and sudden cardiac death associated with the use of various NSAIDs and COX-2 selective agents were then compared. Most of the nonselective NSAIDs increased the relative risk of a cardiac event (Figure 4) compared with the control group. High doses (>25 mg daily) of rofecoxib, indomethacin, naproxen, and diclofenac were associated with an elevated risk of MI and sudden death, whereas celecoxib and ibuprofen were not.

A unique analysis of the risk of cardiac events, including death in patients who had had a previous acute MI, was performed by Gislason et al⁶⁹ in Denmark. In a cohort of ≈ 60 000 patients, the use of the nonselective NSAIDs ibuprofen and diclofenac was fairly common (11% to 17%), whereas only 4% to 5% received the COX-2 inhibitors

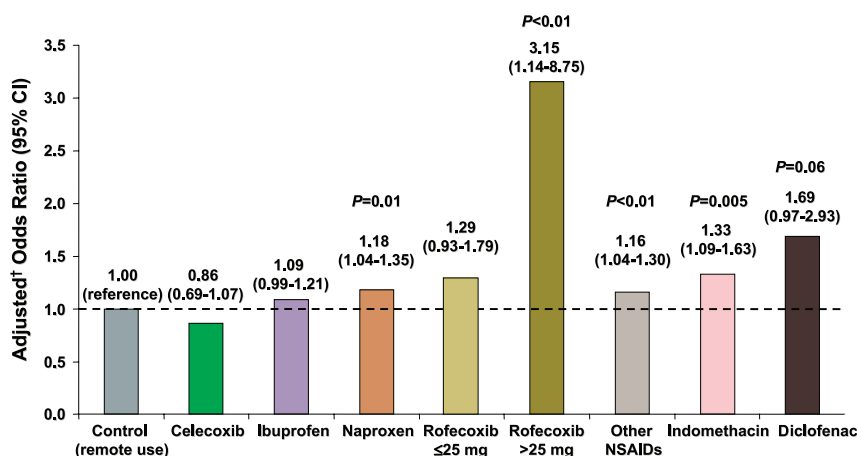


Figure 4. Results of a 2-year observational study in 1.4 million persons administered various NSAIDs in a closed formulary health maintenance organization in California. The relative risk of acute myocardial infarction and sudden CV death was compared with nonusers of NSAIDs and COX-2 inhibitors (control group). Adapted from Reference 68.

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

celecoxib or rofecoxib. In most instances, the duration of exposure to the NSAIDs was <90 days. Using a Cox proportional hazards analysis for hazard ratios of death and rehospitalization for MI, they reported a significant increased risk with use of any nonselective NSAID and the selective COX-2 inhibitors. As was observed in the study by Graham et al,⁶⁸ the risk of cardiac events appeared to be increased with higher doses of the NSAIDs.

A substantial number of observational studies were examined and pooled by McGettigan and Henry⁷⁰ for >1 000 000 patients from cohort and case-control studies. As shown in Table 2, diclofenac, indomethacin, meloxicam, and rofecoxib increased the risk of CV events (primarily acute MI) compared with nonusers of NSAIDs, whereas celecoxib, ibuprofen, naproxen, and piroxicam did not increase the risk of CV events.

One other observational study reported in early 2006 by Chan et al⁷¹ deserves mentioning here, because it was an important analysis of the effects of acetaminophen in the population from the Nurse's Health Study. The study was a prospective cohort of ≈71 000 women between 44 and 69 years of age who had 2041 confirmed CV events during 12 years of observation. Compared with nonusers of NSAIDs or acetaminophen, women with frequent consumption of acetaminophen (>22 days per month) had about the same increased risk of a CV event (risk ratio: 1.35; 95% CI: 1.14 to 1.59) as women who took frequent NSAIDs (risk ratio: 1.44;

95% CI: 1.27 to 1.65). The mechanism for increased CV events in women taking acetaminophen is unknown, but the authors speculated that increases in BP, inhibition of PG synthesis, and impaired endothelial function through depletion of glutathione may play a role.⁷¹

Placebo-Controlled Trials With COX Inhibitors

No long-term clinical trials in patients with arthritis have been placebo controlled because of obvious clinical and ethical issues related to pain management. Thus, little, if anything, is known about the absolute risk of using the nonselective NSAIDs compared with no treatment over time in arthritis or pain management. For the COX-2 selective inhibitors rofecoxib and celecoxib and low doses of the nonselective NSAID naproxen, there are 4 placebo-controlled trials in nonarthritis populations that have received a great deal of attention recently because their safety data were published or announced before their efficacy findings.

In the first reported trial, the Adenomatous Polyp Prevention on Vioxx Trial,⁵ the APTC event rate was 1.50 events per 100 patient-years for rofecoxib 25 mg daily versus 0.78 events per 100 patient-years for placebo; in the Adenoma Prevention With Celecoxib Trial,^{72,73} the combined APTC and heart failure event rate was ≈0.4 events per 100 patient-years for placebo, 0.86 events per 100 patient-years for celecoxib 400 mg daily, and 1.27 events per 100 patient-years for celecoxib 800 mg daily. Finally, in the Prevention of Colorectal Sporadic Adenomatous Polyps Trial,⁷⁴ the estimated rates of adjudicated CV events (MI, stroke, and congestive heart failure) were 0.72 events per 100 patient-years for placebo and 0.94 events per 100 patient-years for celecoxib 400 mg daily. As shown in Table 3, event numbers were quite small in these colonic polyp trials and would not typically be considered definitive by standards of CV clinical trialists. Thus, more robust clinical trials assessing CV events are still needed. At this time, the implications of the findings from the Adenomatous Polyp Prevention on Vioxx, Adenoma Prevention With Celecoxib, and Prevention of Colorectal Sporadic Adenomatous Polyps trials relate primarily to disease prevention and not necessarily to the chronic treatment

TABLE 2. Summary of Observation Findings on the Cardiovascular Risk of Inhibitors of Cyclooxygenase

Drug	Relative Risk of Event*	95% CI
Celecoxib	1.06	0.91 to 1.23
Diclofenac	1.40	1.16 to 1.70
Ibuprofen	1.07	0.97 to 1.18
Indomethacin	1.30	1.07 to 1.60
Meloxicam	1.25	1.00 to 1.55
Naproxen	0.97	0.81 to 1.07
Rofecoxib (<25 mg)	1.33	1.00 to 1.70
Rofecoxib (>25 mg)	2.19	1.69 to 2.91

*Cardiovascular event vs nonuser of NSAIDs (data extracted from Reference 70).

TABLE 3. Cardiovascular Events (Adjudicated) From COX-2 Inhibitor Colonic Polyp Prevention Trials

Name of Trial	N	COX-2 Inhibitor	Placebo Events/N	COX-2 Inhibitor Events/N (Rate per 100 Patient-Years)
APPROVe ⁵	2586	Rofecoxib (25 mg)	26/1299 (0.78)	46/1287 (1.50)*
APC ^{70,71}	2035	Celecoxib (200 mg bid)	7/676 (0.40)	18/683 (0.86)
		Celecoxib (400 mg bid)		23/669 (1.27)†
PreSAP ⁷²	1561	Celecoxib (400 mg qd)	12/628 (0.72)	23/933 (0.94)

APPROVe indicates Adenomatous Polyp PRevention on Vioxx Trial; APC, Adenoma Prevention with Celecoxib Trial; PreSAP, Prevention of colorectal Sporadic Adenomatous Polyps Trial.

*Significant vs the placebo rate.

†Events include CV death, nonfatal MI, nonfatal stroke, and the development of congestive heart failure.

of arthritis pain and inflammation in a patient population for whom placebo is not an option.

Another important finding from the Adenomatous Polyp Prevention on Vioxx and Adenoma Prevention With Celecoxib studies^{5,73,74} pertains to interaction with aspirin. In these studies, aspirin use did not appear to influence the relation of CV event rates among patients with spontaneous colonic polyps who received COX-2 inhibitors and those who received placebo. Thus, if the hypothesis that COX-2 selective inhibitors are thrombogenic because of imbalance between prostacyclin and thromboxane A₂ production was correct,⁷⁵ additional suppression of thromboxane synthesis by aspirin should have improved outcomes with the COX-2 inhibitors relative to placebo compared with outcomes for the nonusers of aspirin. In addition, pharmacoepidemiological studies have shown that the frequency of CV events, including MI and sudden cardiac death, is the same with nonselective NSAIDs that inhibit COX-1 as with COX-2 selective inhibitors.^{68,72}

A fourth placebo-controlled study that examined the CV event rates on an NSAID and COX-2 selective inhibitor was the Alzheimer Disease Anti-Inflammatory Prevention Trial⁷⁶. The study randomly assigned ≈2500 patients over the age of 75 years with a first-degree relative with Alzheimer's disease to placebo, celecoxib (200 mg twice daily), and naproxen (220 mg twice daily). This trial was discontinued prematurely (after 3 years rather than 7 years) because of controversies surrounding the safety of NSAIDs in late 2004. The primary results have not been published at the time of this writing, but early results of the Alzheimer Disease Anti-Inflammatory Prevention Trial have been published in a meta-analysis by Salpeter et al.⁷⁷ Results from the Alzheimer Disease Anti-Inflammatory Prevention Trial show a small but significant increase in adjudicated CV event rates (MI, stroke, and heart failure) with naproxen 220 mg twice daily and similar results for celecoxib 200 mg twice daily compared with placebo.

Coadministration of NSAIDs With Aspirin

The gastroprotective effect of COX-2 inhibitors is partially to totally attenuated if aspirin is used for CV prophylaxis.^{1,21} Aspirin acetylates a single serine residue in the COX-1 (serine 529) channel and permanently inactivates the enzyme. Recent pharmacodynamic studies have demonstrated that the propionic acids ibuprofen and naproxen can prevent the irreversible platelet inhibition induced by

aspirin.^{78,79} Diclofenac was not found to have this interaction.⁷⁹ Furthermore, none of the COX-2 selective inhibitors shown in Table 1 interfere with the binding of aspirin on the COX-1 site of the platelet. Data from retrospective analyses of the Physician's Health Study by Kurth et al⁸⁰ and MacDonald and Weil⁸¹ suggest that the NSAID interference with aspirin on platelet inhibition could result in increased CV events over time. In contrast, Gorman et al⁸² reviewed several other epidemiological studies and found no conclusive evidence for a deleterious impact by NSAIDs on the cardioprotective effects of aspirin.

Perspectives

The data that have accumulated since 1999 underscore the importance of carefully analyzing the benefits versus the risks of traditional NSAIDs and COX-2 selective inhibitors before making therapeutic decisions for the management of chronic forms of arthritis pain and inflammation. In clinical practice, the majority of patients with moderate-to-severe arthritis who might benefit from NSAID or COX-2 therapy are likely to be elderly and, therefore, at higher risk for both gastrointestinal and CV adverse events than their younger counterparts. In addition, many of the older patients may be taking low-dose aspirin and could be using available over-the-counter NSAIDs for pain as well. Selecting a combination of therapies that provides relief from arthritis-related symptoms, minimizes CV risk, and preserves the gastrointestinal mucosa is complex. The data accumulated thus far suggest that certain NSAIDs and COX-2 inhibitors might induce small absolute increases in CV events compared with placebo or nonusers of the NSAIDs. There is also evidence that rofecoxib may uniquely increase CV events relative to NSAIDs, but this finding has not been extended to other COX-2 inhibitors. Other factors to consider for patient safety include the interference of propionic acid NSAIDs, (eg, ibuprofen or naproxen), with the antiplatelet effects of aspirin; direct effects of nonselective NSAIDs and of COX-2 selective inhibitors on fluid retention and BP; differences among these agents with regard to associated gastrointestinal adverse event rates; and the use of coadministration of anti-inflammatory therapies with gastroprotective agents, such as proton pump inhibitors when patients require cardioprotective doses of aspirin.

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