

# Selective COX-2 Inhibitors and Risk of Cardiovascular Events

*Gil Segev, MD*

*Richard J. Katz, MD*

**N**onsteroidal anti-inflammatory drugs (NSAIDs) are prescribed commonly for the treatment of pain and inflammation caused by various musculoskeletal disorders and dysmenorrhea. Nonselective NSAIDs' anti-inflammatory effects appear to be caused by blocking the enzyme cyclooxygenase-2 (COX-2). In addition, nonselective NSAIDs exert both their antiplatelet and detrimental effects on the gastrointestinal mucosa by blocking COX-1.<sup>1</sup> COX-2 inhibitors were developed as a safer alternative to traditional NSAIDs because there was less risk of gastrointestinal ulceration.

Recently, concern that COX-2 inhibitors may contribute to the onset of acute myocardial infarction (MI) and thromboembolic events has led to several trials, which have yielded conflicting results regarding the effect that COX-2-specific inhibitors versus traditional NSAIDs have on cardiovascular events. The Celecoxib Long-term Arthritis Safety Study (CLASS) trial showed no difference in the rate of MI in patients taking a COX-2 inhibitor (celecoxib) and those taking NSAIDs (either ibuprofen or diclofenac).<sup>2</sup> Conversely, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, which compared rofecoxib (a COX-2 inhibitor) with naproxen (a nonselective NSAID), found that MIs were more frequent in patients treated with rofecoxib than in patients treated with naproxen.<sup>3</sup> Was this difference due to a detrimental effect of rofecoxib or a beneficial effect of naproxen due to platelet inhibition? This review article discusses the implications of the CLASS and VIGOR studies and analyzes other studies that examine the association between NSAIDs and MIs as well as other acute thromboembolic events.

## COX ISOFORMS AND MECHANISMS OF ACTION

COX-1 is expressed constitutively within most tissues, where it generates prostaglandins that help maintain physiologic functions, including protection of the gastrointestinal mucosa and vascular homeostasis.<sup>4</sup> The COX-1 isoform is found in vascular smooth-muscle cells and platelets. COX-1 mediates production of

thromboxane A<sub>2</sub>, which promotes vasoconstriction and platelet aggregation.<sup>5</sup> In contrast, the COX-2 isoform is induced primarily at sites of inflammation throughout the body to produce prostaglandins.<sup>6</sup> These prostaglandins include prostacyclin, a potent antagonist of platelet aggregation and a vasodilator. COX-2 expression is increased by cytokines, growth factors, and injury to smooth-muscle cells.<sup>5</sup> Prostacyclin, which is formed by vascular endothelial cells, is part of a homeostatic mechanism that limits the thrombotic response of platelet activation.<sup>7</sup> The vasculature normally maintains a healthy balance between COX-2-mediated prostacyclin and COX-1-dependent thromboxane (Figure 1).

## THEORETICAL EFFECTS OF COX-2 INHIBITION ON THE CARDIOVASCULAR SYSTEM

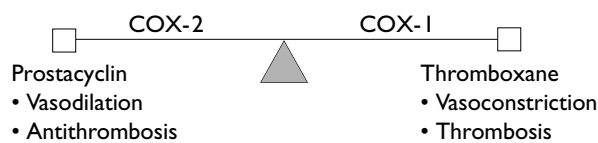
### Theoretical Harmful Effects of COX-2 Inhibition

Most nonselective NSAIDs (excluding aspirin and naproxen) inhibit both COX-1-mediated thromboxane, which contributes to thrombosis, and COX-2-induced prostacyclin, which combats thrombosis (Figure 2). In contrast, the selective inhibition of prostacyclin formation by COX-2-selective NSAIDs interferes with prostacyclin's ability to limit thrombosis and permits the unopposed action of thromboxane. This interference could tip the delicate balance and lead to adverse thrombotic events (Figure 2).

Human endothelial cells can upregulate prostacyclin production many times in response to inflammatory mediators, an effect that is mediated by increased expression of COX-2.<sup>8</sup> Animal models suggest that the interplay between these two prostanoids may be important in the response to endothelial damage. Studies

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*Dr. Segev is a hospitalist at Sibley Memorial Hospital, Washington, DC. At the time this manuscript was submitted, he was an internal medicine resident, George Washington University Hospital, Washington, DC. Dr. Katz is a professor of medicine and director of the division of cardiology, George Washington University School of Medicine, Washington, DC.*



**Figure 1.** Diagram depicting the effects of COX-1 and COX-2 under normal conditions. A balance between thrombotic-antithrombotic effects and vasoconstrictive-vasodilatory effects is maintained. COX = cyclooxygenase.

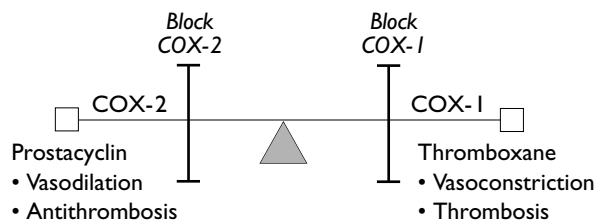
using a rodent model have shown that transfer of the gene that encodes prostacyclin synthase can inhibit neointimal formation in balloon-injured arteries through COX-2-mediated prostanoid synthesis.<sup>9</sup> Similarly, Cheng et al showed injury-induced vascular proliferation and platelet activation are enhanced in mice that are genetically deficient of the prostacyclin receptor. Conversely, injury is decreased in mice genetically deficient in the thromboxane A<sub>2</sub> receptor or treated with a thromboxane antagonist.<sup>10</sup> The increased response to vascular injury was not evident in mice deficient in both receptors. Thus, prostacyclin modulates endothelial interactions in vivo and limits the response to thromboxane A<sub>2</sub>. This interplay is important in evaluating the safety of COX-2 inhibitors.

It has been hypothesized that COX-2-specific inhibitors might increase the risk of cardiovascular thromboembolic events via inhibition of vascular prostacyclin synthesis without inhibition of platelet thromboxane.<sup>11</sup> A recent basic research study supports the potential thrombotic effects of COX-2 inhibitors. Hennen et al demonstrated that the observed increase in time to coronary artery occlusion with aspirin in a canine coronary thrombosis model was abolished with celecoxib.<sup>12</sup>

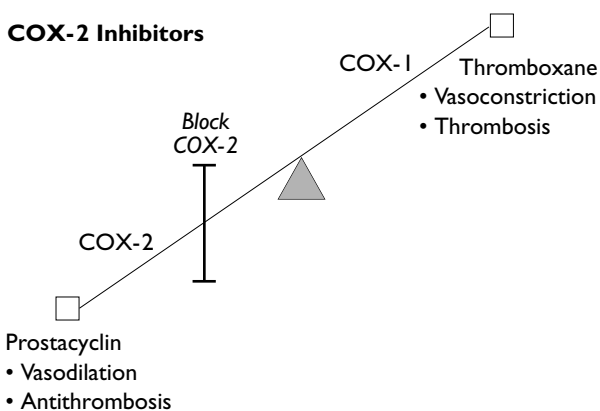
If COX-2 inhibitors are associated with a risk of thrombosis, the risk should be small because of the presence of other endothelium-derived substances, such as nitric oxide, carbon monoxide, and CD39, that protect against thrombosis.<sup>13</sup> However, thrombosis would be more likely to occur in patients who are already at increased risk because of other underlying conditions. In fact, arterial thrombosis occurred after the initiation of celecoxib in 4 patients with lupus anticoagulant.<sup>14</sup>

In addition to maintaining a balance regarding thrombosis, COX inhibitors also can effect the interplay between vasoconstrictive and vasodilatory prostaglandins. COX-1-mediated thromboxane contributes to vasoconstriction, whereas COX-2-induced prostacyclin acts as a potent vasodilator. Nonselective NSAIDs block both of

### Nonselective NSAIDs



### COX-2 Inhibitors



**Figure 2.** A comparison of the effects of nonselective NSAIDs (other than aspirin and naproxen) versus COX-2 inhibitors. Nonselective NSAIDs inhibit both the COX-1 and the COX-2 pathways, maintaining the thrombotic and vasomotor balances. COX-2 inhibitors disrupt this balance, tipping it toward thromboxane-induced thrombosis and vasoconstriction. COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug.

these pathways and, thus, maintain vascular homeostasis. One of the theoretical concerns with COX-2 inhibitors is that their selective blockade of the vasodilator prostacyclin may produce vasoconstriction. Recent studies have demonstrated that up to 80% of prostacyclin production is mediated through the COX-2 isoform.<sup>15-17</sup> In these studies, celecoxib and rofecoxib at therapeutic dosages markedly suppressed prostacyclin synthesis in healthy volunteers. Verma et al showed that COX-2 blockade with rofecoxib, when used at therapeutic doses, did not result in significant changes in endothelial vasodilatory responses.<sup>18</sup> It is possible that if prostacyclin is depressed secondary to COX-2 blockade, upregulation of nitric oxide may preserve vasodilation.

Nitric oxide-induced vasodilation could theoretically be used for clinical benefit by providing patients who take NSAIDs with a nitric oxide donor (NOD). A new

member of this class of medications, termed B-NOD, is available in oral form. B-NOD causes vasodilation, inhibits platelet aggregation, and counteracts thromboxane  $A_2$ .<sup>19</sup> As such, using a NOD in conjunction with a COX-2 inhibitor potentially may maintain vasodilation and minimize thrombosis. B-NOD also may be effective in combating NSAID nephrotoxicity and has been shown to preserve renal prostacyclin levels after administration of NSAIDs.<sup>20</sup>

Aspirin produces irreversible inhibition of platelet COX-1 that is nearly complete and is sustained for at least 48 hours after a single dose.<sup>21</sup> Aspirin has been shown to reduce the incidence of cardiovascular events in patients presenting with acute coronary syndromes and in patients with a history of MI, angina pectoris, or stroke.<sup>22-24</sup> Non-aspirin nonselective NSAIDs are reversible inhibitors of COX-1 and theoretically could have an antithrombotic effect via inhibition of platelet activity. In addition, naproxen inhibits the production of thromboxane by 95% and inhibits platelet aggregation by 88%.<sup>3</sup> This effect is maintained throughout the dosing interval.<sup>25</sup> Therefore, naproxen also may have a cardioprotective effect similar to aspirin (Figure 3).

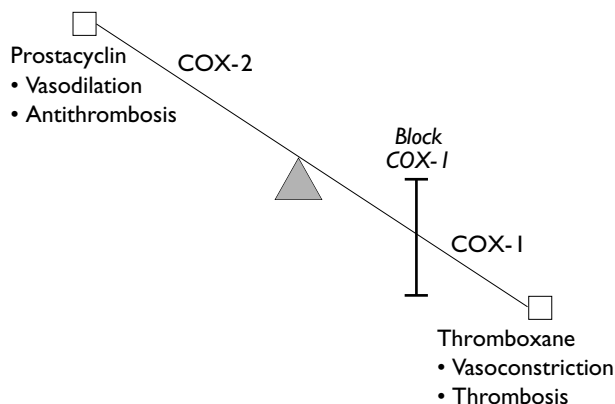
#### Theoretical Beneficial Effects of COX-2 Inhibition

Although there is concern about the potentially negative effects that COX-2 inhibitors may have on vascular homeostasis, there also are theoretical benefits derived from these medications. COX-2 inhibitors potentially may combat atherosclerosis by inhibiting inflammation, in part by blocking prostaglandin  $E_2$  production. Additionally, COX-2 inhibitors may protect against acute cardiovascular events. Thrombosis is thought to occur when overactive macrophages release collagenase, thus breaking down the fibrin coat of atherosclerotic plaques.<sup>26</sup> Because such macrophages express high levels of COX-2, these enzyme inhibitors should reduce macrophage activity and thus may have a cardioprotective effect.

#### RECENT CLINICAL TRIALS ASSESSING COX-2 INHIBITORS AND CARDIOVASCULAR EVENTS

##### CLASS Study

The CLASS trial was a randomized controlled trial designed primarily to compare the gastrointestinal safety of celecoxib (400 mg twice daily, a dose 4 times that recommended for osteoarthritis and twice that for rheumatoid arthritis) with 2 other NSAIDs, diclofenac (75 mg twice daily) and ibuprofen (800 mg three times daily). The patients in the trial were permitted to take aspirin for cardiovascular prophylaxis in doses up to 325 mg daily. A total of 8059 adult patients (73% with



**Figure 3.** Theoretical benefit of aspirin and naproxen. Mostly COX-1 is inhibited, tipping the balance toward prostacyclin-induced vasodilation and antithrombosis. COX = cyclooxygenase.

osteoarthritis and 27% with rheumatoid arthritis) were assigned to receive either celecoxib or either one of the NSAIDs; 22% of the patients were taking aspirin. The annualized incidence of MI (fatal and nonfatal) among all patients, including those taking aspirin, did not show any statistically significant differences regardless of treatment group (celecoxib, 0.5%; diclofenac, 0.2%; ibuprofen, 0.5%).<sup>2</sup>

The rates of hypertension and edema were significantly higher in the ibuprofen group than in the celecoxib and diclofenac groups; the rates of heart failure were similar in the 3 groups. The overall incidence of cardiovascular events and the incidences of cerebrovascular events and MI were similar in the 2 treatment groups. The cohort of patients not taking aspirin for cardiovascular prophylaxis showed no differences in cardiovascular events between the celecoxib and NSAID groups.<sup>2</sup>

Use of aspirin for cardiovascular prophylaxis should be considered in patients taking NSAIDs or COX-2 inhibitors. The CLASS study indicates that the gastrointestinal protective effects that are garnered by the use of celecoxib instead of ibuprofen or diclofenac are lost when patients take aspirin concurrently. In the CLASS trial, the observed incidences of symptomatic ulcers and/or ulcer complication were not significantly different in patients taking celecoxib versus those patients taking NSAIDs with concomitant low-dosage aspirin. Conversely, the cohort that was not taking aspirin showed a significant reduction in gastrointestinal complications with celecoxib use instead of traditional NSAIDs. Given that taking aspirin negates much of the gastrointestinal protection offered by COX-2

inhibitors, some may argue that in patients taking aspirin, it may be more cost effective to use a traditional NSAID (in conjunction with a proton-pump inhibitor) rather than a COX-2 inhibitor.<sup>2</sup>

### **VIGOR Study**

The VIGOR trial compared rofecoxib (50 mg daily) with naproxen (500 mg twice daily) in 8076 patients with rheumatoid arthritis who were treated for a median of 9 months. Aspirin use was not permitted in the study, and patients requiring aspirin for cardiac reasons were excluded from the trial. The 2 drugs had similar efficacy for the treatment of rheumatoid arthritis, but the relative risk (RR) of confirmed gastrointestinal events was lower with rofecoxib (RR, 0.5 [95% confidence interval {CI}, 0.3–0.6];  $P < 0.001$ ). Both drugs were similarly effective. The incidence of gastrointestinal perforation, gastrointestinal hemorrhage, or symptomatic peptic ulcer was 4.5 per 100 patient-years in the naproxen group and 2.1 per 100 patient-years in the rofecoxib group, a difference of 54% (absolute reduction, 2.4%).<sup>3</sup>

During an interim analysis, excessive cardiovascular adverse effects were found in 1 group. The safety board recommended adjudication of vascular events and 98 cases (65/4047 from the rofecoxib group and 33/4029 from the naproxen group) were investigated. Of these, 45 patients (46 events) in the rofecoxib group and 20 patients (20 events) in the naproxen group were found to have serious cardiovascular adverse events (MI, unstable angina, resuscitated cardiac arrest, sudden or unexplained death, cardiac thrombus, ischemic stroke, and transient ischemic attacks) with a RR of 2.38 for rofecoxib patients developing such an event.<sup>27</sup> The annualized incidence of MI in the rofecoxib group was 4 times that of the naproxen group (0.4% versus 0.1%).<sup>3</sup> The 2 groups had similar rates of death from cardiovascular causes.

From this study, 3.9% of patients met the US Food and Drug Administration criteria for the use of aspirin for secondary cardiovascular prophylaxis. These patients accounted for 38% of the patients who had a MI. It was unclear whether the difference in MI incidence was due to detrimental prothrombotic effects of rofecoxib or a beneficial antithrombotic effect from naproxen, or even both.<sup>3</sup>

Naproxen has significant antiplatelet effects, with mean platelet aggregation inhibition of 88% compared with 92% mean inhibition for 81-mg aspirin.<sup>25</sup> Ibuprofen does not share this quality and has a platelet aggregation inhibition of only 20%. This evidence of an antiplatelet effect suggests that naproxen may have a beneficial antithrombotic effect.

### **Database Studies of COX-2 Inhibitors and Cardiovascular Events**

Mukherjee et al<sup>27</sup> compared the overall rate of cardiovascular events in COX-2 inhibitor trials (including the VIGOR and CLASS studies and 2 smaller studies) with the rate observed in a large placebo group of a meta-analysis. The annualized rate of MI was found to be higher in the COX-2 inhibitor group. Unfortunately, the design of this study raises major concerns.

The study is a flawed comparison because there were important baseline differences among the different trial groups. The CLASS study was composed primarily of osteoarthritis patients, while the VIGOR study was composed primarily of rheumatoid arthritis patients at increased cardiovascular risk. The outcomes of the patients with arthritis receiving COX-2 inhibitors were compared with that of healthy patients receiving placebo in primary prevention trials. These inconsistencies cloud the interpretation of the results of this study.<sup>27</sup>

Konstam et al<sup>11</sup> compared the incidence of thrombotic events in patients receiving rofecoxib with the incidence of those receiving placebo or nonselective NSAIDs. More than 28,000 patients in 23 studies (osteoarthritis, rheumatoid arthritis, Alzheimer's, and chronic low back pain trials), representing more than 14,000 patient-years at risk, were analyzed for differences in cardiovascular thrombotic event rates. The investigators found no excess in the number of thrombotic events in those treated with rofecoxib compared with those receiving placebo or NSAIDs other than naproxen. They did find, however, a significantly higher rate of thrombotic events in patients treated with rofecoxib compared with naproxen.<sup>11</sup> They concluded that naproxen's cardioprotective antiplatelet effect likely was responsible for the differences between the 2 groups.

### **Case-Controlled Studies of Naproxen and Cardiovascular Events**

Three recent large case-controlled studies present convincing evidence that patients treated with naproxen have a decreased incidence of MI compared with patients receiving NSAIDs other than naproxen or those not receiving NSAIDs.<sup>28</sup> The most likely mechanism is naproxen's ability to block platelet aggregation.<sup>25</sup>

Watson et al<sup>29</sup> showed that patients with rheumatoid arthritis and a current prescription for naproxen had a reduced risk of acute major thromboembolic events (MI, sudden death, and stroke) relative to those without a naproxen prescription in the past year.<sup>29</sup> The incidence of MI was lower in those taking naproxen (odds ratio [OR], 0.57 [95% CI, 0.31–1.06];  $P = 0.07$ ). The

incidence of all thromboembolic events was significantly lower in those taking naproxen compared with those not taking NSAIDs (OR, 0.61 [95% CI, 0.39–0.94];  $P=0.03$ ).

Rahme et al compared chronic naproxen versus non-aspirin NSAID use and hospitalization for acute MI among elderly Canadian men and women.<sup>30</sup> They found the risk of hospitalization for acute MI to be lower among long-term and current users of naproxen than among long-term users of other non-aspirin NSAIDs (OR, 0.65 [95% CI, 0.48–0.97]).

Solomon et al examined non-aspirin NSAIDs and found that NSAID use in general was not associated with an increase or decrease in the risk of acute MI, but use of naproxen was associated with a 16% to 20% reduction in the risk of MI when compared with non-users (OR, 0.84 [95% CI, 0.72–0.98];  $P=0.03$ ).<sup>31</sup>

## SUMMARY

The nonspecific NSAIDs aspirin and naproxen appear to provide protection against harmful cardiovascular events. Three case-controlled studies have affirmed the cardioprotective effect of naproxen, most likely due to its proven antiplatelet activity. Most other NSAIDs have not been found to provide benefit or risk for cardiovascular events.

The epidemiologic studies analyzing the cardiovascular impact of COX-2 inhibitors have yielded conflicting results. The CLASS study showed no difference in the risk of cardiovascular thromboembolic events between celecoxib and ibuprofen/diclofenac. Conversely, the VIGOR study showed an increased risk of MIs in patients taking the COX-2 inhibitor rofecoxib compared with those taking the nonselective NSAID naproxen.

These conflicting results may be explained by significant differences in study design. Most of the patients in the CLASS trial were being treated for osteoarthritis, whereas the VIGOR study group was composed primarily of rheumatoid arthritis patients. Patients with rheumatoid arthritis may have an increased risk of thrombotic events and, therefore, directly comparing these study groups may lead to flawed conclusions.<sup>32</sup> Also, it should be noted that patients in the VIGOR study were restricted from taking aspirin, whereas those in the CLASS study were allowed to take concurrent aspirin. This difference in study design also may have had an impact on cardiovascular events in the different groups.

Although COX-2 inhibitors generally exhibit class effects, rofecoxib and celecoxib display different levels of COX-2 selectivity, which may contribute to the different study outcomes. Rofecoxib is 80 times more selective for COX-2 compared with COX-1, while cele-

coxib only has 9 times the affinity for COX-2 over COX-1.<sup>33</sup> Celecoxib, which has less COX-2 selectivity, theoretically may maintain a better balance between the COX-1 and COX-2 pathways. A greater divergence between the COX pathways seen with rofecoxib may account for the positive results of the VIGOR study.

Another significant difference between the two studies is the comparison NSAID used for the control group. The CLASS study compared celecoxib versus ibuprofen and diclofenac, 2 nonselective NSAIDs that have no evidence of cardioprotective effects. In contrast, the VIGOR study compared rofecoxib with naproxen, an NSAID that likely confers cardioprotection. The VIGOR data may be explained by a beneficial effect of naproxen rather than a detrimental effect of the COX-2 inhibitor rofecoxib. This hypothesis is further supported by Konstam et al's study,<sup>11</sup> which shows no increased risk of cardiovascular events when rofecoxib was compared with placebo or NSAIDs other than naproxen.

## CONCLUSION

Given these study design limitations, the current data indicates that, despite the theoretical concern of disrupting the homeostatic balance of anti- and prothrombotic prostaglandins, COX-2 inhibitors have not been shown to increase the risk of atherothrombotic events compared with placebo and with NSAIDs other than naproxen. The available data on COX-2 inhibitors and cardiovascular risk is based on retrospective subgroup analysis of noncardiovascular clinical trials. Long-term prospective randomized controlled trials with appropriate outcomes (eg, cardiovascular events, death) are needed to clarify concerns of cardiovascular safety in patients taking COX-2 inhibitors. Patients using COX-2 inhibitors who are at risk for atherothrombotic events should take aspirin concurrently. Unfortunately, the gastrointestinal protective effect of COX-2 inhibitors is minimized in patients who take aspirin.

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