CARDIOVASCULAR EFFECTS OF COX-2 INHIBITORS: A REVIEW OF THE LITERATURE

Craig D. Cox, PharmD, BCPS, Brad L. Stanford, PharmD, BCOP, James P. Tsikouris, PharmD, Michael J. Peeters, PharmD, BCPS, and Gary Meyerrose, MD

After reviewing this article, the reader should be able to:

I Understand the possible mechanisms of action for the cardiovascular side effects of the various COX-2 inhibitors.
I Identify which patients are appropriate for COX-2s.
I Understand the relationship of dose and duration of the prescribed drugs to the incidence of cardiovascular side effects.
I Understand the distinct characteristics of the various COX-2 inhibitors.

Abstract

When cyclooxygenase-2 (COX-2) inhibitors (coxibs) came on the market, they were expected to provide a treatment alternative to nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) for patients who were at risk for gastrointestinal (GI) complications. For more than five years, coxibs have been prescribed to millions of patients for the treatment of arthritis, acute pain, Alzheimer’s disease, and cancer prevention.

Until recently, a favored GI profile was the focus of this class of medications, when new data surfaced suggesting an increased risk of cardiovascular (CV) events in patients taking coxibs. In multiple trials and analyses, the incidence of CV events has been higher with coxibs than with placebo and other nonselective NSAIDs. With differences also reported between the individual coxibs, the question of a drug class effect has been raised.

Although an explanation for these adverse effects has not yet been determined, several potential theories relate to physiological mechanisms, drug selectivity or structure, doses and duration of clinical trials, or the influence of underlying disease states. Until long-term, randomized clinical trials are completed to determine CV risks, it will be difficult to resolve this current controversy regarding the safety of coxibs. As long as the thrombotic risk with coxibs remains unclear, only patients who meet defined criteria for their use should receive them at the lowest possible dose for the shortest period of time.

Introduction

The adverse effects of cyclooxygenase-2 (COX-2) inhibitors (coxibs) have demanded attention over the past few years, and questions have been raised about their safety. Coxibs arrived on the market in 1998 with the hope of offering a treatment with a lower risk of gastrointestinal (GI) toxicity compared with other nonsteroidal anti-inflammatory drugs (NSAIDs). Even though clinical trials show that coxibs carry a lower risk of GI adverse drug events (ADEs), none of the literature supports the superior efficacy of coxibs over NSAIDs.

In view of these findings, coxibs should be reserved for patients with the greatest risk for GI complications. Unfortunately, this recommendation has not been followed. In a 2002 review of patterns of coxib use, one third of patients taking these agents were found to be at the lowest risk of having NSAID-induced complications. Clearly, the coxib medication class has been overprescribed, possibly because of the influence of direct marketing in the U.S. With millions of patients...
receiving these medications, often inappropriately, the safety of these drugs is a concern.

Results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial\(^4\) suggested an increased risk of cardiovascular (CV) events in patients taking coxibs. Since then, conflicting results regarding CV risk have come to light in many studies, including randomized clinical trials,\(^6–8\) case-control and cohort studies,\(^10–15\) and pooled meta-analyses.\(^16–27\) On the basis of these findings, rofecoxib (Vioxx, Merck) and valdecoxib (Bextra, Pfizer) have been withdrawn from the market in the U.S.

Even with mounting evidence in clinical trials, an explanation for the increased CV risk has remained elusive.\(^28–30\) With celecoxib (Celebrex, Pfizer) still available for sale in the U.S. and with two other coxibs—lumiracoxib (Prexige, Novartis) and etoricoxib (Arcoxia, Merck)—being considered for Food and Drug Administration (FDA) approval, the question of whether one coxib agent has a greater risk than others must be answered.

Figure 1 presents a timeline of events involving the coxibs. A complete list of coxibs and their distinct characteristics are provided in Table 1.

The following review summarizes the major clinical studies that have raised concerns about coxibs and the risk of CV disease along with a discussion of the possible causes of these increased risks.

### Randomized Clinical Trials

A summary of randomized trials of coxib therapy is presented in Table 2.

### Rofecoxib

In the VIGOR trial, rofecoxib (Vioxx) was compared with naproxen in 8,076 patients with rheumatoid arthritis (RA) over a median of nine months.\(^4\) The dose of rofecoxib in this trial (50 mg daily) was twice the FDA-approved dose recommended for chronic RA analgesia and anti-inflammatory use. Similar efficacy was found between treatments, with rofecoxib causing significantly fewer GI events; however, rofecoxib demonstrated an increased risk of CV events over naproxen.

Patients receiving rofecoxib were 2.4 times more likely to experience a major CV event, such as myocardial infarction (MI), unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, an ischemic stroke, or transient ischemic attacks.\(^23\) The incidence of MI was also five times greater with rofecoxib (0.5%) than with naproxen (0.1%).\(^4\) The reported differences in CV events could not be explained by any of the baseline patient characteristics measured. Acetylsalicylic acid (ASA) was not allowed in this trial, although 4% of patients did meet the FDA’s criteria for using ASA to prevent a CV event.\(^4\) Of the MIs experienced by patients, 38% of them occurred within this small group of patients who were not taking ASA but who should have been. In both subgroups (for whom aspirin was indicated and not indicated), the naproxen group revealed a lower risk of stroke and MI, a lower risk of serious thrombotic events, and lower rates of adjudicated events compared with the rofecoxib group.

The VIGOR trial was the first to raise concerns about CV ADEs with rofecoxib. At the time, the differences in CV events were considered to be a result of a cardioprotective effect of naproxen rather than an increased risk from rofecoxib.

After many observational studies\(^10–13,31–33\) and meta-analyses\(^16–18,23\) revealing conflicting results of CV risk, safety data from the Adenomatous Polypl Prevention on Vioxx (APPROVe) trial were released. Over a period of three years, rofecoxib 25 mg daily was compared with placebo in 2,586 patients with a history of colorectal adenomas to assess the ability of rofecoxib to prevent the recurrence of colorectal polyps.\(^6\) The rofecoxib patients had a greater risk of developing a confirmed thrombotic event compared with the patients receiving placebo (relative risk \(RR\), 1.92; 95% confidence interval \(CI\), 1.19–3.11; \(P = .008\)).

Differences in cardiac events (MI, unstable angina, and sudden death from cardiac causes) were also reported. Rofecoxib was associated with a 2.8 times greater risk of a CV event. These observed differences did not occur until 18 months after the start of the trial, and they continued to grow as treatment continued. Unlike patients in the VIGOR trial,\(^4\) patients in the APPROVe trial were allowed to take ASA, although only 20% of patients reported taking it. ASA use did not demonstrate a lower risk of either thrombotic or CV events.

A history of symptomatic atherosclerotic CV disease and diabetes were the only two baseline characteristics that appeared to affect the results; each showed a higher relative risk for the rofecoxib patients than for the placebo patients. With the APPROVe results, rofecoxib had shown an increase in CV risk when compared with both naproxen and placebo. As a result, Merck voluntarily withdrew rofecoxib from the U.S. marketplace on September 30, 2004.

### Celecoxib

In the Celecoxib Long-term Arthritis Safety Study (CLASS), celecoxib was compared with conventional NSAIDs (ibupro-
patients (1.3%) from that of the NSAID group (1.2%). Even thrombotic effects did not differ significantly in the celecoxib (400 mg twice daily) were used in this study. Compared with placebo in 2,035 patients. Patients were treated for coxib 200 mg twice daily and 400 mg twice daily when compared with placebo, and patients taking 800 mg/day had a 2.3 times higher incidence of a CV event compared with those taking placebo. Approximately 30% of patients took ASA during the study, but ASA had no impact on the frequency of CV events in any of the three groups. A similar trial, Prevention of Sporadic Adenomatous Polyps (PreSAP), compared celecoxib 400 mg daily to placebo in reducing the occurrence of adenomatous polyps in the colon and rectum. After more than 1,500 patients were treated for 33 months, the incidence of CV events did not differ between groups (RR, 1.1; 95% CI, 0.6–2.3). About 15% of the study’s patients took ASA, but this did not affect the frequency of CV events in either group. Although the reasons for the conflicting results between the PreSAP and APC trials cannot be easily explained, the celecoxib dosing differed in the trials. Celecoxib 400 mg once daily (in PreSAP) does not provide the same consistent exposure to the drug during a 24-hour period as celecoxib 200 mg twice daily (in APC). A more consistent concentration of drug may have contributed to the increased risk of CV events noted in the APC trial over the PreSAP trial, even with the same 400-mg total daily dose.

The Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT) compared celecoxib 200 mg twice daily with naproxen 220 mg twice daily and placebo. The purpose was to evaluate a potential decrease in the incidence of Alzheimer’s disease with NSAID therapy. Although the projected accrual was 2,625 patients, a preliminary safety review demonstrated no increase in cerebrovascular or CV events in the celecoxib arm. However, patients receiving naproxen showed an increased risk of CV events over placebo. In late December 2004, as a result of the naproxen results, the trial was stopped early. Despite the conflicting results of these trials involving celecoxib, the FDA required that a warning of a potential increased CV risk be added to package labeling on the basis of the APC findings.

**Valdecoxib**

Valdecoxib (Bextra), unlike rofecoxib and celecoxib, has not been subjected to long-term randomized trials to assess either its safety or efficacy; however, two short-term trials that evaluated valdecoxib for treating acute pain following coronary artery bypass graft (CABG) surgery are available. A double-blind, controlled clinical trial was performed to compare a combination of parecoxib (Dynastat, Pharmacia/Pfizer) and valdecoxib to placebo. Parecoxib is the pro-drug of valdecoxib, and it is administered only parenterally. Sequential parecoxib/valdecoxib was given to 462 patients for 14 days with a 30-day follow-up period after therapy was completed. One MI (0.7%) occurred in the control group, and five MIs (1.6%) occurred in the treatment group. A similar trend was seen with cerebrovascular disorders; the treated patients experienced a higher incidence of cerebrovascular events (2.9%) than the controls (0.7%) did. The sample size might have been inadequate to demonstrate statistical significance.

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### Table 1 Basic Differences between COX-2 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Normal Dose*</th>
<th>Selectivity† (COX-2/COX-1)</th>
<th>Half-Life (Hours)</th>
<th>Chemical Structure</th>
<th>Market Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vioxx (rofecoxib)</td>
<td>12.5–50 mg q.d.</td>
<td>272</td>
<td>15–18 hours</td>
<td>Sulfone</td>
<td>Withdrawn in September 2004</td>
</tr>
<tr>
<td>Celebrex (celecoxib)</td>
<td>100–400 mg q.d.</td>
<td>30</td>
<td>6–12 hours</td>
<td>Sulfonamide</td>
<td>Still available in U.S.</td>
</tr>
<tr>
<td>Bextra (valdecoxib)</td>
<td>10–20 mg q.d.</td>
<td>61</td>
<td>6–10 hours</td>
<td>Sulfonamide</td>
<td>Withdrawn in April 2005</td>
</tr>
<tr>
<td>Arcoxia (etoricoxib)</td>
<td>30–120 mg q.d.</td>
<td>344</td>
<td>20–26 hours</td>
<td>Sulfone</td>
<td>Approved in Europe, not available in U.S.</td>
</tr>
<tr>
<td>Prexige (lumiracoxib)</td>
<td>100–400 mg q.d.</td>
<td>700</td>
<td>2–6 hours</td>
<td>Arylacetic acid derivative</td>
<td>Not available in U.S. or Europe</td>
</tr>
</tbody>
</table>

* Dose ranges for the treatment of acute pain, arthritis, Alzheimer’s disease, and prevention of colon cancer.
† COX-2/COX-1 represents the relative cyclooxygenase selectivity of each of the respective drugs that have been derived from in vitro whole blood assays and may differ slightly from other published values.
b.i.d. = twice daily; COX = cyclooxygenase; q.d. = once daily.

A second randomized, double-blind trial involved 10 days of treatment and 30 days of follow-up in 1,500 patients. Three groups of patients were assigned to receive one of these therapies:

- intravenous (IV) parecoxib for three days, followed by oral valdecoxib through 10 days
- IV placebo, followed by oral valdecoxib for 10 days
- placebo for 10 days

The incidence of CV events was significantly greater with parecoxib and valdecoxib (2%) than with placebo (0.5%) (RR, 3.7; 95% CI, 1.0–13.5; \( P = .03 \)). All CV events occurred equally during the treatment and follow-up periods. In each trial, patients began ASA therapy immediately following surgery.

The CABG trials, which involved very-high-risk patients, led to an FDA-mandated boxed warning cautioning against the use of valdecoxib in patients after CABG surgery. Thereafter, in April 2005, after a review of an excessive number of case reports of severe skin reactions, valdecoxib was withdrawn from the market.

Lumiracoxib

Only one long-term trial has been published with lumiracoxib (Prexige), and it is the only coxib trial adequately powered to measure the incidence of CV events. Over one year, the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) compared the safety and efficacy of lumiracoxib with naproxen and ibuprofen for the treatment of OA. No significant differences between lumiracoxib and naproxen (RR, 1.77; 95% CI, 0.82–3.84; \( P = .1471 \)) or ibuprofen (RR, 0.66; 95% CI, 0.21–2.09; \( P = .4833 \)) were noted in the incidence of MIs. In addition, no differences were observed in the patients taking ASA.

Etoricoxib

Limited data exist for the evaluation of the long-term safety effects of etoricoxib (Arcoxia) as well. The Etoricoxib Diclofenac Gastrointestinal Evaluation (EDGE) study compared etoricoxib 90 mg once daily with diclofenac 50 mg three times daily in more than 7,000 patients over a nine-month period. There were 26 confirmed CV events (0.72%) in the etoricoxib patients and 19 events (0.54%) in the diclofenac group. Thirty percent of patients were receiving concurrent ASA. No differences were found among patients taking ASA, but the non-ASA subgroup had more MIs in the patients taking etoricoxib.

As noted in these randomized clinical trials, the risk of CV events was increased with rofecoxib, celecoxib, and valdecoxib but was not clearly evident with lumiracoxib and etoricoxib.

Observational, Case–Control, Retrospective Cohort Studies

Global intrigue has surrounded the randomized clinical trials just described. For the many analyses that have been forthcoming, most have compared rofecoxib and celecoxib with other nonselective NSAIDs (e.g., ibuprofen, diclofenac, and naproxen). For rofecoxib, many studies have demonstrated an increased risk of CV or cerebrovascular events, when compared with either placebo or nonselective NSAIDs, but other studies have not shown such findings. Fewer studies have demonstrated an increased risk with celecoxib, and several head-to-head studies found that rofecoxib carried a higher risk in direct comparison with celecoxib.

It is difficult to draw conclusions from these data, considering the multiple variables that might have affected the results, such as the dose, the duration, and comparator agents. It appears that rofecoxib may be associated with a greater risk of CV events than celecoxib.

Meta-analyses

Rofecoxib

Meta-analyses have been performed to evaluate both rofecoxib and celecoxib independently. The first pooled analysis of patient data from participants in phase IIb–V rofecoxib clinical trials of four weeks or more in duration compared rofecoxib with placebo, naproxen, and non-naproxen NSAIDs. Data from 23 studies, involving multiple disease states and more than 28,000 patients, were analyzed.

The Antiplatelet Trialists’ Collaboration (APTC) endpoint consists of the combined incidence of the following:

- CV events, hemorrhage, and death from unknown causes
- nonfatal MI
- nonfatal stroke

Results were as follows:

- rofecoxib versus placebo (RR, 0.84; 95% CI, 0.51–1.38)
- rofecoxib versus non-naproxen NSAIDs (RR, 0.79; 95% CI, 0.40–1.55)
- rofecoxib versus naproxen (RR, 1.69; 95% CI, 1.07–2.69)

The differing results were explained by the perceived cardio-protective effect of naproxen, similar to the conclusion of the VIGOR trial. No differences were found in the duration of the study or in the rofecoxib dose.

A second analysis was conducted to evaluate 5,435 patients with OA from eight studies that compared rofecoxib with placebo and non-naproxen NSAIDs. With findings similar to those of the aforementioned analysis, no differences in the combined endpoints from the Antiplatelet Trialists’ Collaboration were found between any of the groups receiving placebo, non-naproxen NSAIDs, or rofecoxib.

A third and more recent meta-analysis evaluated 18 randomized, controlled trials and 11 observational studies. More than 25,000 patients were evaluated, and the combined relative risk for the rofecoxib patients was more than twice that of...
controls (RR, 2.24; 95% CI, 1.24–4.02; \( P = .007 \)). In this analysis, the authors reported that by the year 2000, the increased risk of MI with rofecoxib had become evident, and it has remained constant since then.

These findings could not be explained by the naproxen-cardioprotection theory. Comparator agents, doses, and duration of the trials did not appear to affect the trial results.

### Celecoxib

Several meta-analyses, varying in size and study design, have been performed with celecoxib.\textsuperscript{19–22} Three of these analyses revealed no increase in CV events with this agent, compared with placebo or other NSAIDs,\textsuperscript{19–21} although one analysis in 2006 did find an increase in the rate of MIs with celecoxib.\textsuperscript{22}

In one analysis, OA and RA trials of four weeks or more in...
duration were considered, allowing data from 13 New Drug Application (NDA) studies and the Celecoxib Long-term Arthritis Safety Study (CLASS) and Successive Celecoxib Efficacy and Safety Study (SUCCESS) postmarketing trials to be evaluated.\textsuperscript{19} A total of 31,879 patients were included in the study analyses. When the same endpoints from the Antiplatelet Trialists' Collaboration were used, no significant differences were found between celecoxib and NSAIDs (RR, 1.06; 95% CI, 0.70–1.61; \( P = .79 \)) or placebo (RR, 0.85; 95% CI, 0.23–3.15; \( P = .81 \)). No differences were seen with the use of ASA or in terms of the underlying arthritis type.

In another meta-analysis, the authors compared tolerability of various doses of celecoxib and associated adverse events in patients with arthritis.\textsuperscript{20} They evaluated 31 clinical trials, ranging from 2 to 52 weeks, that had been performed in patients with OA and RA. No difference in the number of MI events was seen with celecoxib (0.18%) versus the comparators (0.12%) (RR, 1.4; 95% CI, 0.88–2.2).

White et al. recently reported their findings of an analysis of celecoxib in more than 41,000 patients at the 2006 American College of Cardiology meeting.\textsuperscript{21} For adjudicated events, celecoxib versus placebo (RR, 1.11; 95% CI, 0.47–2.67; \( P = .81 \)) or other NSAIDs (RR, 0.90; 95% CI, 0.60–1.33; \( P = .59 \)) did not show an increase in CV events. These findings were similar to the two prior analyses.

Caldwell et al. evaluated four placebo-controlled trials involving more than 4,000 patients. Several outcomes, including composite CV events and MI rates with celecoxib, were assessed.\textsuperscript{22} For the combined CV events, celecoxib did not show an increased risk (OR, 1.38; 95% CI, 0.91–2.1); however, for MI rates only, it did show an increased risk (OR, 2.26; 95% CI, 1.0–5.1).

In a secondary analysis performed by the same authors, similar results were found in a comparison of celecoxib and other NSAIDs. Unlike prior analyses, this was the first analysis to find an increased risk with celecoxib. Another analysis, which included the VIGOR and CLASS trials, evaluated the risk of CV events associated with both rofecoxib and celecoxib.\textsuperscript{23} Rofecoxib demonstrated an increased risk when compared with naproxen. In addition, when results of the VIGOR trial were compared to those of a placebo group in a meta-analysis of more than 23,000 patients, the annual MI rate for rofecoxib was significantly higher (0.74% vs. 0.52% for naproxen, respectively) (\( P = .04 \)).

### Combined Rofecoxib and Celecoxib

Another analysis, which included the VIGOR and CLASS trials, evaluated the risk of CV events associated with both rofecoxib and celecoxib.\textsuperscript{23} Rofecoxib demonstrated an increased risk when compared with naproxen. In addition, when results of the VIGOR trial were compared to those of a placebo group in a meta-analysis of more than 23,000 patients, the annual MI rate for rofecoxib was significantly higher (0.74% vs. 0.52% for naproxen, respectively) (\( P = .04 \)).
Unlike earlier reports showing no increased risk of CV events in the CLASS trial, when the authors used the same placebo comparator, the annual MI rate with celecoxib (0.80%) was significantly higher than with placebo (0.52%) (P = .02).

Other Coxibs

Few analyses have been performed to assess the risk of CV events with other coxibs. Two pooled analyses of randomized trials of valdecoxib were performed; one analysis included 8,000 patients with RA or OA, and the other included 3,000 patients with RA.24,25 No differences in the incidence of thrombotic events were found between the valdecoxib and comparator groups.

Pooled data were evaluated from more than 6,700 patients receiving etoricoxib in all phase 2, 3, and 4 studies lasting four weeks or more.27 Etoricoxib showed no increased risk of CV events over that for placebo (RR, 1.1; 95% CI, 0.32–3.81), naproxen (RR, 1.70; 95% CI, 0.91–3.18) or other non-naproxen NSAIDs (RR, 0.83; 95% CI, 0.26–2.64).

In a meta-analysis of 22 randomized clinical trials evaluating lumiracoxib, no increased risk of CV events, as defined by the Antiplatelet Trialists’ Collaboration, occurred compared with placebo (RR, 0.88; 95% CI, 0.34–2.25), naproxen (RR, 1.49; 95% CI, 0.94–2.36) or non-naproxen NSAIDs (RR, 0.83; 95% CI, 0.26–2.64).

Considering these analyses, the risk of CV events appears to be highest in patients taking rofecoxib compared with other coxibs. Many of the trials differed in study design, methods of recording safety outcomes, and comparator agents, thereby making it difficult to draw firm conclusions. It is noteworthy that the primary outcomes and study power were based on the assessment of GI risk, a slowing progression of Alzheimer’s disease, treatment of arthritic pain, or the secondary prevention of colorectal cancer—but not CV risk. Therefore, differences noted in these clinical studies and other analyses should be evaluated cautiously. Long-term, randomized clinical trials that are powered to show CV risks are urgently needed.

Possible Explanations for Cardiovascular Outcomes

Physiology of COX-2 Inhibition on the Cardiovascular System

As we have begun to understand the physiological mechanisms of COX isoenzymes, an appreciation of the potential negative effects of inhibiting the COX-2 enzyme has been recognized.42,43 Theoretical adverse effects include problems with salt and water balance, wound healing, and thrombosis. The COX-1 enzyme is responsible for thromboxane production, the promotion of platelet adhesion, and vasoconstriction; the COX-2 enzyme results in prostacyclin formation and the consequential inhibition of thrombosis and vasodilation (Figure 2).

Ideally, these enzyme systems maintain a homeostatic balance between bleeding and thrombosis. When nonselective NSAIDs are given, they inhibit both COX-1 and COX-2 activity, and a balance of thrombotic activity is maintained. By contrast, when coxibs are given, they are selective to the COX-2 enzyme, affecting the ability of prostacyclin to limit thrombosis and allowing thromboxane-unopposed thrombosis to occur. These physiological effects may account for a portion of the increase in CV and renovascular events associated with coxibs.

Dose-Related Effects

The VIGOR trial used doses of rofecoxib 50 mg daily,4 whereas the APPROVe trial used doses of only 25 mg daily.6 Among observational studies, a greater risk was observed with doses of rofecoxib above 25 mg/day than with doses of 25 mg/day or less.12,13,15 In a study by Graham et al., doses of 25 mg/day or less produced a 47% greater risk of MIs compared with celecoxib, whereas doses higher than 25 mg/day produced more than three times the risk.15

In two trials by Solomon et al.12 and Levesque et al.,13 rofecoxib doses higher than 25 mg were more likely to cause a CV event when compared with other NSAIDs. For celecoxib, the Adenoma Prevention with Celecoxib (APC) trial used two doses (200 mg twice daily and 400 mg twice daily), and an increased CV risk was evident at the higher doses.7 Other trials using both doses did not show an increase in CV events, but other factors such as patient population and study duration may account for this.34,36,38

It is interesting that in the Prevention of Sporadic Adenomatous Polyps (PreSAP) trial (which was similar in design to the APC trial), a dose of 400 mg once daily did not demonstrate an increased risk. This may be a result of the more constant serum concentration of drug seen when it is given twice daily, as compared with once daily.

In the CABG trials, very high doses of valdecoxib were used. In each instance, there was a clear increase in CV events.8,9 It is difficult to draw firm conclusions, because graduated doses were not examined and all patients were at high risk for CV events when they began the study.

Lumiracoxib and etoricoxib have not been studied in large multiple, long-term trials evaluating different dosage strategies, thus making these coxibs difficult to assess. However, high doses of both agents were used in the TARGET® and EDGE41 trials; neither trial showed an increased risk of CV events.

From this limited information, it appears that higher doses of either rofecoxib or celecoxib may be associated with a greater risk of CV events.

Duration of Trials

The clinical trials that showed an increased risk of CV events had a common trend in terms of their length:

- The association of rofecoxib with CV events was seen in trials completed over nine and 33 months, with evidence of risk beginning at 18 months.4,6
- For celecoxib, the APC trial demonstrated a risk by 33 months.7
coxib and etoricoxib—have half-lives of two to six hours and agents without a demonstrated increased CV risk—lumiracoxib—that have been demonstrated to date. This limitation may offset the lack of CV endpoint differences in these large trials. The data for lumiracoxib and etoricoxib are scant, and drugs cannot exclusively account for the development of CV risk, whereas those with moderate half-lives have shown this shortest and longest half-lives have not shown an increased CV risk. COX-2 Selectivity

The three agents that have demonstrated an increased CV risk—rofecoxib, celecoxib, and valdecoxib—have half-lives ranging from six to 18 hours (Table 1). In contrast, the two agents without a demonstrated increased CV risk—lumiracoxib and etoricoxib—have half-lives of two to six hours and 20 to 26 hours, respectively. Thus, the coxibs with the shortest and longest half-lives have not shown an increased CV risk, whereas those with moderate half-lives have shown this risk.

In view of these conflicting data, the half-life of this class of drugs cannot exclusively account for the development of CV events. The data for lumiracoxib and etoricoxib are scant, and this limitation may offset the lack of CV endpoint differences that have been demonstrated to date.

COX-2 Selectivity

COX-2 selectivity (i.e., the agent’s specificity and affinity for the COX-2 enzyme over the COX-1 enzyme) may also be a factor in the relationship of coxibs to the risk of CV events. Clearly, rofecoxib has demonstrated the greatest risk, whereas celecoxib has shown an increased risk only sporadically. In assessments of COX-2 selectivity, rofecoxib has a higher selectivity (with a COX-2:COX-1 ratio of 272 to 1) than celecoxib (with a ratio of 30 to 1) (see Table 1). However, etoricoxib and lumiracoxib are the most COX-2 selective (with ratios of 344 to 1 and 700 to 1, respectively); neither agent has shown a comparable increased CV risk, as with rofecoxib and celecoxib.

We emphasize that the classification of nonselective NSAIDs and coxibs on the basis of their COX enzyme selectivity is controversial. Some nonselective NSAIDs, such as meloxicam (Mobic, Boehringer Ingelheim) and diclofenac potassium (Cataflam, Novartis), have a COX-2 selectivity that is comparable to that of celecoxib.

Renovascular Effects

Coxibs cause various renovascular effects, including volume retention and increases in blood pressure (BP). Reports of changes in BP and edema involving coxibs have provided conflicting results. Patients taking rofecoxib showed an increased risk for edema and hypertension, when compared with users of celecoxib, nonselective NSAIDs, and non-NSAIDs in multiple studies. Valdecoxib has had this effect, when compared with placebo, in a pooled analysis of five clinical trials. Conversely, lumiracoxib and etoricoxib had similar effects on BP and edema, when compared with nonselective NSAIDs.

A meta-analysis of more than 45,000 patients showed that coxibs cause elevations of systolic and diastolic BP when compared with NSAIDs and placebo. Within this analysis, rofecoxib showed an even greater risk of BP elevations than celecoxib. Reasons for these differences are not clearly understood, but the unique pharmacokinetics of each coxib may play a role. More details are presented next under the heading “Metabolism and Chemical Structure.”

Thus, even though rofecoxib and valdecoxib have been associated with the greatest risk of CV events and appear to have the greatest chance of causing renovascular events, no firm correlation in clinical trials has been shown.

Metabolism and Chemical Structure

All coxibs have similar mechanisms of action for COX-2 inhibition, but each one has a unique pharmacokinetic profile. Only rofecoxib does not undergo extensive metabolism via a cytochrome P450 (CYP 450) system. Instead, its metabolism is mediated through the reduction of cytosolic enzymes, with less than 1% of the drug being recovered unchanged in the urine. All other coxibs are eliminated predominantly by the CYP 450 system, either 3A4 (valdecoxib, etoricoxib) or 2C9 (celecoxib, valdecoxib, and lumiracoxib). In addition, enterohepatic recirculation is unique to rofecoxib and has been reported in both rat and human studies, with resultant biphasic serum peaks of drug.
metabolism is unclear, these disparities might contribute to the variations in renal and cardiovascular effects. For instance, after cytosol reductase metabolism, rofecoxib may compete for the metabolism of aldosterone, with resulting increases in both sodium and fluid retention as well as the promotion of vascular remodeling. The consequences include an increased risk of edema, hypertension, and acute decompensation of chronic heart failure.

Alternatively, celecoxib does not compete for cytosol reductase; instead, it works as a carbonic anhydrase inhibitor and provides a diuretic effect in the kidney that counteracts potential increases in hypertension and edema. It is noteworthy that these renovascular outcomes that have been reported in multiple studies and analyses occur more often with rofecoxib than with any other coxib.

The chemical structure of each coxib, excluding lumiracoxib, is classified as either a sulfone or a sulfonamide (Table 1). Lumiracoxib is classified as an arylacetic acid derivative. Its unique structure contributes to its very short half-life (two to six hours), compared with the other coxibs. The shorter half-life may decrease the overall exposure time of this drug in circulation and may potentially reduce thromboembolic risk. To gain a better understanding of their role in the development of these adverse effects, we need further investigations into the relevance of these differences in pharmacokinetic parameters and chemical structures.

**Study Populations**

In evaluating randomized, controlled trials, we find a diversity of patient populations, with a wide range of risks for CV events at the baseline evaluation (from 4% to 100%) (Table 2). Even though the impact of the degree of baseline CV risk on the results is still debatable, the use of valdecoxib in CABG trials involved very-high-risk patients, and an increased CV risk was found.

Rofecoxib has demonstrated an increased CV risk in patients with RA and in patients with a history of colorectal adenomas. Celecoxib has also shown an increased CV risk in patients with colorectal adenomas. However, no large, long-term, controlled trials have been done to evaluate the efficacy and safety of valdecoxib, lumiracoxib, and etoricoxib in patients with RA or colorectal adenomas.

This raises an interesting question regarding specific study populations. It appears that patients with RA and a history of colorectal adenoma are at an increased risk of CV disease when they use coxibs for a long duration (more than nine months), whereas patients with OA or Alzheimer’s disease are not at an elevated risk.

RA is a significant risk factor in the development of CV disease, independent of other patient factors. Vascular endothelial growth factor (VEGF) can be detected in the serum, synovial tissue, and fluids of patients with RA. In these patients, VEGF is a marker for angiogenesis, which allows for the formation of new blood vessels and permits a supply of nutrients and oxygen that helps with the perpetuation of synovitis.

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**Figure 3** The COX-2 enzyme stimulates tumor angiogenesis by activating multiple pathways. It is responsible for converting arachidonic acid to prostaglandin H2 (PGH2), which is later converted to PGE2, PGI2, and thromboxane A2 (TXA2). PGE2 leads to the production or activation of vascular endothelial growth factor (VEGF), survival signal pathway (Akt), anti-apoptotic pathway (Bcl-2), vascular integrin (α5β3), matrix metalloproteinase (MMP-2 and MMP-9), interleukin-12 (IL-12), IL-8, and epidermal growth factor-receptor (EGF-R). PGI2 leads to an increase in endothelial cell (EC) sprouting and vascular permeability. TXA2 production leads to an increase in endothelial cell migration. (Adapted with permission from Gately S, et al. *Semin Oncol* 2004;31[Suppl 7]:2–11. © 2004, Elsevier.)
several reports, VEGF concentrations were elevated in the serum of RA patients compared with healthy controls and OA patients. VEGF concentrations appear to be higher in patients with early RA and correlate well with disease activity and severity.

Similar findings have been published regarding patients with colorectal cancer. As normal tissue progresses to become an adenoma, to nonmetastatic cancer, and then to metastatic cancer, the concentration of VEGF continues to increase. In patients with only colorectal adenomas, however, there is debate about the significance of VEGF concentrations.

Although increased VEGF levels are observed in patients with RA and colorectal adenomas, these levels are not significantly elevated in uncomplicated cases of either OA or Alzheimer’s disease. Therefore, VEGF may play an important role in the development of CV consequences, as observed with coxib use.

Ideally, when coxibs are used, the level of COX-2 enzyme expression is increased; this is directly related to the inflammatory component of the disease state studied. In cancer patients, COX-2 has been recognized as an upstream stimulator of VEGF production and is beneficial for maintaining endothelial cell integrity (Figure 3).

Thus, if COX-2 activity is blocked with a coxib, VEGF concentrations may decrease, making endothelial cells prone to apoptotic cell death. Cell death would result in damage to the basement membrane, thereby leading to the initiation of the coagulation cascade, resulting in platelet activation, aggregation, and finally thrombus formation.

Studies have shown conflicting results on the effects of COX-2 inhibition and the effects on endothelial cell activity. It seems reasonable that the risk of these events might be even greater in patients with cells that have been exposed to stress or previous damage.

It is interesting that in randomized, active-controlled studies, the incidence of arterial thromboembolic events was increased with the use of a VEGF antagonist, bevacizumab (Avastin, Genentech), when combined with chemotherapy for the treatment of colon cancer. The incidence of both overall arterial thromboembolic events and CV arterial events was higher in patients receiving bevacizumab (4.4% vs. 1.9%) than in the active controls (2.1% vs. 1.0%).

The increased risk of CV disease, as seen with rofecoxib and celecoxib in the APPROVe and APC trials, may be related to the underlying disease process. In both studies, all patients had a history of colorectal adenomas and had undergone a previous colonoscopy to remove any adenomas that were present before they were enrolled in the study. Therefore, the enrolled patients did not have any adenomas and would not have been expected to have increased levels of VEGF at baseline; however, patients with a history of colorectal adenomas or polyp removal, such as these study populations, generally have a colorectal adenoma recurrence rate of approximately 20% per year. Given this assumption, then, about 60% of patients could have developed an adenoma by the third year during these clinical trials. Patients with recurrent adenomas would have the potential to have increased VEGF concentrations and to be at an increased risk of CV events when given coxibs.

This theory is further supported by the observed delay in CV events in both the rofecoxib and celecoxib randomized clinical trials. As was noted, the risk with rofecoxib was not seen until 18 months of therapy, whereas this risk with celecoxib was seen after 2.5 to three years of therapy. Hence, for the first 18 months, patients may not have had an increased CV risk, because they were adenoma-free at the time of their inclusion in the study. However, more patients may have developed adenomas as the study progressed and, as a consequence, could have experienced an increased number of CV events.

Unfortunately, because the data on cancer prevention from these studies are not yet available, this explanation is merely a theory. Yet it suggests that effects on vascular and inflammation markers such as VEGF may contribute to the increased CV risk seen with the coxibs.

**Conclusion**

Currently, only celecoxib is available in the U.S.; lumiracoxib and etoricoxib are under investigation. Rofecoxib was removed from the market in September 2004 because of its increased risk of CV events, and valdecoxib was removed in April 2005 as a result of a combination of increased risk of CV events and severe dermatologic conditions. It is clear that drugs within this class of medications have shown an increased risk of CV toxicity, but it is not yet possible to affirm that this is a class effect. One concern related to the current data is that the TARGET trial—the only study powered to detect an increased risk of CV events—did not show an increased risk with lumiracoxib compared with other NSAIDs.

Another matter for debate is that the nonselective NSAIDs that were used as comparator agents in these trials also lacked data on CV safety; however, results from randomized controlled trials, observational studies, case–control studies, and meta-analyses have all demonstrated some increased risk with celecoxib, rofecoxib, and valdecoxib.

It is also difficult to attribute the risks to a specific entity; that is, higher doses and a duration of therapy of more than nine months appear to pose the greatest risk, but the effects of COX-2 selectivity, the half-lives of the drugs, the effects of ASA, and other factors still need to be defined.

In addition, the baseline CV risk has not clearly been shown to be a factor in the development of CV events, although underlying disease states—specifically, RA and colorectal adenomas—may play a role. We will be able to gain a further understanding of the role of these conditions on CV outcomes after all of the data on cancer prevention have been released.

To date, the question of safety with coxibs is still unanswered. In view of the undefined risks of thrombosis with coxibs, only patients who meet defined criteria for their use should receive them at the lowest possible dose for the shortest period of time.
References


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Continuing Education Questions for Physicians and Pharmacists

P&T® 2006;31(10):604–615

ACPE Program #079-999-06-022-H01

Expiration Date: October 31, 2007

TOPIC: Cardiovascular Effects of COX-2 Inhibitors: A Review of the Literature

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Multiple Choice

Select the one correct answer.

1. What is the half-life of celecoxib?
   a. 15–18 hours
   b. 6–12 hours
   c. 6–10 hours
   d. 20–26 hours

2. According to the APPROVe trial, what is the number needed to harm by rofecoxib with regard to cardiovascular (CV) events?
   a. 15
   b. 63
   c. 167
   d. 1,000

3. Which of the following has the highest COX-2 selectivity?
   a. rofecoxib
   b. valdecoxib
   c. etoricoxib
   d. lumiracoxib

4. According to CABG No. 1 and CABG No. 2, what is the approximate risk of CV events associated with valdecoxib compared with placebo in CABG patients?
   a. 1%
   b. 2%
   c. 4%
   d. 8%

5. Coxibs have been studied in randomized clinical trials to treat all of the following conditions except:
   b. arthritis.
   c. cancer prevention.
   d. depression.

6. Which of the following medications is currently available for use in the U.S.?
   a. rofecoxib
   b. celecoxib
   c. valdecoxib
   d. etoricoxib

7. Which trial was the first to raise concerns about CV adverse events with coxibs?
   a. APPROVe
   b. CLASS
   c. APC
   d. VIGOR

8. A meta-analysis of the COX-2 inhibitors concludes that the risk of CV events appears to be the highest in patients taking:
   a. celecoxib.
   b. rofecoxib.
   c. valdecoxib.
   d. lumiracoxib.

9. The COX-2 enzyme converts arachidonic acid to PGH₂, which subsequently leads to:
   a. decreased epithelial cell migration.
   b. decreased epithelial cell sprouting.
   c. decreased vascular permeability.
   d. increased VEGF.

10. All of the coxibs undergo extensive metabolism via a cytochrome P450 system except:
    a. lumiracoxib.
    b. celecoxib.
    c. rofecoxib.
    d. etoricoxib.
CE Registration and Evaluation Form

Date of publication: October 2006
Title: Cardiovascular Effects of COX-2 Inhibitors: A Review of the Literature
Authors: Craig D. Cox, PharmD, BCPS, Brad L. Stanford, PharmD, BCOP, James P. Tsikouris, PharmD, Michael J. Peeters, PharmD, BCPS, and Gary Meyerrose, MD
Submission deadline: October 31, 2007
ACPE Program #079-999-06-022-H01

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Answer Sheet

Please fill in the box next to the letter corresponding to the correct answer

1. a □ b □ c □ d □ 6. a □ b □ c □ d □
2. a □ b □ c □ d □ 7. a □ b □ c □ d □
3. a □ b □ c □ d □ 8. a □ b □ c □ d □
4. a □ b □ c □ d □ 9. a □ b □ c □ d □
5. a □ b □ c □ d □ 10. a □ b □ c □ d □

Evaluation

Rate the extent to which: 

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<th>Very High</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
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1. Objectives of this activity were met          □  □  □  □  □
2. You were satisfied with the overall quality of this activity □  □  □  □  □
3. Content was relevant to your practice needs □  □  □  □  □
4. Participation in this activity changed your knowledge/attitudes □  □  □  □  □
5. You will make a change in your practice as a result of participation in this activity □  □  □  □  □
6. This activity presented scientifically rigorous, unbiased, and balanced information □  □  □  □  □
7. Individual presentations were free of commercial bias □  □  □  □  □
8. Adequate time was available for Q&A □  □  □  □  □
9. Which ONE of the following best describes the impact of this activity on your performance:
   □ This program will not change my behavior because my current practice is consistent with what was taught.
   □ This activity will not change my behavior because I do not agree with the information presented.
   □ I need more information before I can change my practice behavior.
   □ I will immediately implement the information into my practice.
10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)
    □ Discuss new information with other professionals     □ Consult the literature
    □ Discuss with industry representative(s)              □ Participate in another educational activity
    □ Other ___________________________________________ □ None

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