Nonsteroidal anti-inflammatory drugs (NSAID) inhibit cyclooxygenase (COX) enzymes, which exist in at least two isoforms, COX-1 and COX-2. Aspirin and older agents in this class are nonselective inhibitors of both COX-1 and COX-2. Newer agents termed “coxibs” are selective inhibitors of COX-2. Among the NSAID, only aspirin has been proven to significantly reduce cardiovascular risk, primarily through inhibition of COX-1-mediated platelet aggregation. It has been suggested that other nonselective agents, especially naproxen, may provide some lesser degree of cardioprotection, but conclusive evidence is lacking. Conversely, there are concerns that the COX-2 inhibitors may increase cardiovascular risk. However, mechanisms for this potentially adverse cardiovascular effect are unknown, and it is becoming increasingly clear that our understanding of the role of COX-2 in cardiovascular function is incomplete. Some studies have demonstrated a potentially beneficial effect of COX-2 on cardiovascular function that could be negated by COX-2 inhibition, while other studies have reported improved endothelial function with COX-2 inhibitors. Additionally, the impact of combined therapy with aspirin and other COX inhibitors is not yet clear. This article will review the studies that have examined these issues. (J Am Coll Cardiol 2004;43: 519–25) © 2004 by the American College of Cardiology Foundation

Nonsteroidal anti-inflammatory drugs (NSAID) are a heterogeneous class including aspirin and various other nonselective and selective inhibitors of cyclooxygenase (COX). Aspirin is the only NSAID used for prevention and treatment of coronary heart disease (CHD). For primary prevention, aspirin has been shown to reduce the risk of cardiovascular events by 15% and myocardial infarction (MI) by 30% (1). The third U.S. Preventive Services Task Force recommends low-dose aspirin for primary prevention in patients at risk (2). Aspirin has also been shown to reduce the risk of recurrent MI or other thrombotic vascular events by approximately 25% (3). Practice guidelines from the American College of Cardiology and American Heart Association recommend chronic low-dose aspirin for secondary cardiovascular prevention (4).

Many cardiovascular patients have comorbidities such as musculoskeletal disorders that necessitate the use of other NSAID. These nonaspirin nonsteroidal anti-inflammatory drugs (NANSAID) are among the most widely prescribed drugs in the world, with an estimated 100 million prescriptions in 1986 (5). Nonprescription use is also common. Use of selective COX-2 inhibitors or “coxibs” has increased dramatically since their introduction in 1999 (6). During 2001, COX-2 inhibitors ranked sixth among the top 10 therapeutic classes prescribed in the U.S. with over $4.7 billion in annual sales (7).

With the widespread use of NANSAID, several important clinical questions have emerged. First, studies have reported an increased risk of cardiovascular events with COX-2 inhibitors. Second, it has been suggested that some nonselective NANSAID, particularly naproxen, may have cardioprotective effects. Finally, there has been debate over the wisdom of combining aspirin with other NSAID. This article will review the basis for these concerns and recent trials addressing these issues.

**PHARMACOLOGY OF NSAID**

The major mechanism of action for NSAID as shown in Figure 1 is inhibition of the COX enzymes that catalyze the conversion of arachidonic acid to various eicosanoids including thromboxane and various prostaglandins (5,8–10). Cyclooxygenase exists in at least two isoforms designated as COX-1 and COX-2 (9–11). The two isoforms are encoded by different genes and have unique patterns of expression. The COX-1 isozyme is essential for the maintenance of normal physiologic states in many tissues including the kidney, gastrointestinal tract, and platelets. For example, COX-1 activation in the gastric mucosa leads to prostacyclin production, which is cytoprotective (12). The COX-2 isozyme is induced by various inflammatory stimuli including cytokines, endotoxins, and growth factors. The COX enzymes play an important role in cardiovascular homeostasis. Thromboxane A₂, which is primarily synthesized in platelets through COX-1 activity, causes platelet aggregation, vasoconstriction, and smooth muscle proliferation. Conversely, prostacyclin (PG I₂) synthesis, which is largely mediated by COX-2 activity in macrovascular endothel-
treatment of inflammation and pain (16). This class includes rofecoxib and celecoxib, which are widely used in the U.S.; etoricoxib, which was recently introduced in the United Kingdom; and agents under development, such as lumiracoxib and meloxicam. Because platelets primarily express the COX-1 isozyme, these drugs would not be expected to possess antithrombotic properties. However, even among these agents, the relative selectivity toward COX-2 varies. For example, both rofecoxib and etoricoxib have greater COX-2 selectivity than celecoxib. In addition, the role of COX-2 in cardiovascular function remains unclear. Recently, concerns have been raised that some COX-2 inhibitors may actually promote thrombosis.

**Selective COX-2 Inhibitors and Cardiovascular Outcomes**

Studies have suggested a possible link between COX-2 inhibitors and increased cardiovascular risk (Table 1). To date, no completed prospective trials have specifically addressed this issue. However, clinical trials of COX-2 inhibitors designed to examine gastrointestinal outcomes have reported cardiovascular events. Unfortunately, the findings from these clinical trials, which used different COX-2 inhibitors, have been inconsistent.

Concerns of potentially adverse cardiovascular effects initially resulted from clinical studies involving rofecoxib. The Vioxx Gastrointestinal Outcomes Research study (VIGOR) (17) compared rofecoxib 50 mg daily to naproxen 500 mg twice daily in 8,076 rheumatoid arthritis patients. Patients with recent cardiovascular events or those taking aspirin were excluded. The primary end point was upper gastrointestinal events. Unexpectedly, the study found a higher incidence of MI with rofecoxib compared with naproxen (0.4% vs. 0.1%; 95% confidence interval, 0.1% to 0.6%). Investigators were uncertain whether the increased MI risk was due to a detrimental effect of rofecoxib or the prohibition of aspirin use. Further analysis showed that the 4% of patients who qualified as aspirin candidates for secondary cardiovascular prevention accounted for 38% of the MIs. Among patients without indications for aspirin prophylaxis, MI rates were not significantly different between rofecoxib and naproxen. These findings led investigators to suggest the observed differences could be due to a protective naproxen effect. Gastrointestinal bleeding, a potential indicator of antithrombotic effects, was significantly lower with rofecoxib as compared with naproxen (relative risk, 0.4; 95% confidence interval, 0.3 to 0.6).

In contrast with VIGOR, the Celecoxib Long-term Arthritis Safety study (CLASS) found no increased risk of MI (18). This trial included 8,059 patients with osteoarthritis or rheumatoid arthritis. The primary end point was upper gastrointestinal toxicity. Patients were treated with celecoxib 400 mg twice daily or another nonselective COX

![Diagram](Image)

**Figure 1.** Action of nonsteroidal anti-inflammatory drugs (NSAID). Arachidonic acid, liberated from membrane phospholipids in response to multiple stimuli, is converted to prostaglandin H2 by cytosolic prostaglandin G/H syntheses (cyclooxygenase [COX]-1 and -2). Prostaglandin H2 is converted by tissue-specific isomerases to multiple prostanoids. Aspirin and other nonselective nonaspirin nonsteroidal anti-inflammatory drugs (NANSAID) inhibit both COX-1 and -2, whereas coxibs selectively inhibit COX-2.

### Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>CHD</td>
<td>coronary heart disease</td>
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<tr>
<td>CLASS</td>
<td>Celecoxib Long-term Arthritis Safety study</td>
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<tr>
<td>COX</td>
<td>cyclooxygenase</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>NANSAID</td>
<td>nonaspirin nonsteroidal anti-inflammatory drugs</td>
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<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>VIGOR</td>
<td>Vioxx Gastrointestinal Outcomes Research study</td>
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inhibitor (ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily). The trial was not placebo-controlled, and naproxen was not evaluated. Aspirin in daily doses up to 325 mg for cardioprotection was permitted and used by approximately 20% of patients in both the celecoxib and NANSAID groups. The two treatment groups showed no statistically significant difference in MI rates or total cardiovascular events, although numerically there were more MIs in the celecoxib group. Although no differences in cardiovascular outcomes relative to aspirin use were apparent, the trial was not designed to examine differences between aspirin users and nonusers. Total bleeding rates were higher with NANSAID compared with celecoxib (6.0% vs. 3.1%, respectively). The impact of combined aspirin-NANSAID use on bleeding could not be determined due to the low rate of aspirin use.

It should be noted that the two comparator agents in CLASS, diclofenac and ibuprofen, have relatively weak antiplatelet effects (6). Effects of combined therapy with aspirin and various NANSAID on serum thromboxane B₂ concentrations, an indicator of platelet COX-1 enzyme activity and platelet aggregation, have been studied in healthy volunteers (8). Concomitant administration of ibuprofen, but not diclofenac or rofecoxib, antagonized the platelet-inhibiting effects of aspirin. This finding is furthered supported by a recent epidemiological study of 7,107 patients with cardiovascular disease (19). Concomitant ibuprofen therapy blunted aspirin’s cardioprotective effect resulting in a twofold increased risk of death and a 75% increased risk of cardiovascular disease. These findings raise concerns about concomitant aspirin-ibuprofen use and suggest differences in the modulation of aspirin’s cardioprotection by various NANSAID.

Cardiovascular outcomes have also been reported from a clinical trial of etoricoxib, a highly selective COX-2 inhibitor (20). This 12-week efficacy trial included 816 patients with rheumatoid arthritis. Patients received etoricoxib 90 mg daily, naproxen 500 mg twice daily, or placebo. Patients with known cardiovascular disease were excluded. However, patients were allowed to take aspirin up to 100 mg daily. There were two confirmed adjudicated cardiovascular events in the trial, both in patients taking etoricoxib. One clinically significant bleeding event was reported in a naproxen patient.

### Table 1. Summary of Selected NSAID Studies Evaluating CV Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>n</th>
<th>History of CHD</th>
<th>ASA Allowed*</th>
<th>Cardiovascular Outcomes</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical Studies of COX 2 Inhibitors</strong></td>
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<tr>
<td>VIGOR (17)</td>
<td>RA</td>
<td>8,076</td>
<td>4% known CHD Excluded patients with recent CV events</td>
<td>No</td>
<td>Increased MI rate with rofecoxib vs. naproxen CV death rates similar</td>
</tr>
<tr>
<td>CLASS (18)</td>
<td>OA/RA</td>
<td>8,059</td>
<td>Not excluded</td>
<td>Yes ≤325 mg</td>
<td>Similar CV event rates for celecoxib and NANSAID</td>
</tr>
<tr>
<td>Matsumoto et al. (20)</td>
<td>RA</td>
<td>816</td>
<td>Excluded</td>
<td>Yes ≤100 mg</td>
<td>2 CV events with etoricoxib vs. 0 events with naproxen</td>
</tr>
<tr>
<td><strong>Pooled Analyses of COX 2 Inhibitor Clinical Trials</strong></td>
<td></td>
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<tr>
<td>Reicin et al. (21)</td>
<td>OA</td>
<td>5,435</td>
<td>12% known CHD</td>
<td>No</td>
<td>Similar CV event rates with rofecoxib, NANSAID, and placebo</td>
</tr>
<tr>
<td>Konstam et al. (22)</td>
<td>Mixed</td>
<td>28,000</td>
<td>Not excluded</td>
<td>Variable among trials</td>
<td>Increased CV events with rofecoxib vs. naproxen but not other NANSAID</td>
</tr>
<tr>
<td><strong>Observational Studies of COX 2 Inhibitors</strong></td>
<td></td>
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<tr>
<td>Mandani et al. (24)</td>
<td>Mixed</td>
<td>66,964</td>
<td>Not excluded</td>
<td>Yes</td>
<td>Similar CV event rates for celecoxib, rofecoxib, naproxen, other NANSAID vs. controls</td>
</tr>
<tr>
<td><strong>Observational Studies of Naproxen and Other NANSAID</strong></td>
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<tr>
<td>Solomon et al. (25)</td>
<td>Mixed</td>
<td>4,425 cases 17,700 controls</td>
<td>Excluded</td>
<td>No</td>
<td>Decreased MI rate with naproxen but other NANSAID vs. nonusers</td>
</tr>
<tr>
<td>Watson et al. (26)</td>
<td>RA</td>
<td>809 cases 2,285 controls</td>
<td>Excluded</td>
<td>No</td>
<td>Decreased CV events with naproxen</td>
</tr>
<tr>
<td>Rahme et al. (27)</td>
<td>Mixed</td>
<td>4,163 cases 14,160 controls</td>
<td>Not excluded unless recent event</td>
<td>Yes</td>
<td>Decreased MI rate with naproxen vs. other NANSAID</td>
</tr>
<tr>
<td>Ray et al. (28)</td>
<td>Mixed</td>
<td>181,441 cases 181,441 controls</td>
<td>Not excluded</td>
<td>Yes</td>
<td>Decreased MI rate with naproxen vs. ibuprofen</td>
</tr>
</tbody>
</table>

*Undisclosed nonprescription aspirin (ASA) use cannot be ruled out.

CHD = coronary heart disease; COX = cyclooxygenase; CV = cardiovascular; GI = gastrointestinal; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drugs; NANSAID = nonaspirin nonsteroidal anti-inflammatory drugs; OA = osteoarthritis; RA = rheumatoid arthritis.
In response to these conflicting results, several secondary analyses have been performed to examine cardiovascular risk. Mukherjee et al. (6) performed additional analyses on data from VIGOR and CLASS (6). The annualized MI rates for both trials were compared with those of 23,407 placebo patients not taking aspirin from a meta-analysis (1) of four published primary prevention trials. As compared with the annualized MI rate of 0.52% for the placebo patients, the annualized MI rates were increased with both rofecoxib (0.74%, p = 0.04) and celecoxib (0.80%, p = 0.02).

Another study examined the risk of thrombotic cardiovascular events among patients receiving rofecoxib, and nonselective NANSAD (ibuprofen, diclofenac, or nabumetone) or placebo. Safety was assessed using a database of 5,435 participants in eight rofecoxib osteoarthritis clinical trials (21). After a median treatment duration of 3.5 months, no differences in cardiovascular risk were found between rofecoxib, comparator nonselective NSAID, and placebo.

A pooled data analysis was conducted from 23 rofecoxib clinical trials involving over 28,000 patients and 14,000 patient-years of risk (22). Indications for rofecoxib included rheumatoid arthritis, osteoarthritis, back pain, and Alzheimer’s prevention. The primary outcome was a combined vascular end point similar to that used in the Antiplatelet Trialists Collaboration (3) including cardiovascular hemorrhagic and unknown deaths, nonfatal MI, and nonfatal strokes. In this pooled analysis (22), no excess thrombotic events were found when rofecoxib was compared with placebo or a nonselective NANSAD other than naproxen (diclofenac, ibuprofen, nabumetone). However, the risk of thrombotic events was higher with rofecoxib compared with naproxen alone (relative risk, 1.69; 95% confidence interval, 1.07 to 2.69). The study investigators attributed the difference to a protective effect of naproxen, noting that near-complete inhibition can be achieved throughout the dosing interval with naproxen doses of 500 mg twice daily.

White et al. (23) further analyzed the CLASS data to assess cardiovascular risk for celecoxib and other NONSAID. The analyses included 3,987 persons randomized to celecoxib and 3,981 persons randomized to a comparator. Rates for serious cardiovascular events defined as MI, stroke, cardiovascular death, and peripheral events were similar for celecoxib and the comparators ibuprofen or diclofenac for all patients and an aspirin subgroup. No significant differences were found for combined event rates or individual event rates including MI.

A large Canadian retrospective cohort study (24) examined the risk of MI with various NSAID. The study included 15,271 celecoxib patients, 12,156 rofecoxib patients, 5,669 naproxen patients, 33,868 NANSAD patients, and 100,000 randomly selected control patients. In contrast with other studies, no increased risk of MI was found with either COX-2 inhibitor. Additionally, no decreased risk of MI was observed with naproxen or other NANSAD.

### NONSELECTIVE NANSAD AND CARDIOVASCULAR OUTCOMES

Observational case-control studies have suggested a possible cardioprotective effect with naproxen (Table 1) (25–28). A retrospective study using a New Jersey Medicare and Medicaid patient database compared NANSAD use among 4,425 patients hospitalized for MI and 17,700 controls (25). Overall, NANSAD users had the same MI risk as nonusers. However, naproxen use was associated with a significant reduction in MI risk (odds ratio, 0.84; 95% confidence interval, 0.72 to 0.98; p = 0.03).

A retrospective study from the United Kingdom examined the risk of acute thromboembolic cardiovascular events (MI, sudden death, and stroke) in rheumatoid arthritis patients receiving naproxen (26). A total of 809 cases were matched with up to four control patients each. Compared with patients with no documented naproxen use during the year before a thrombotic event, naproxen within the previous 30 days significantly reduced the risk of an event (odds ratio, 0.61; 95% confidence interval, 0.39 to 0.94). Conversely, no protective effect was seen with other NANSAD combined or with ibuprofen or diclofenac alone.

A retrospective Canadian study compared naproxen to other NANSAD for secondary MI prophylaxis in patients ≥65 years of age hospitalized for MI (27). The study included 4,163 cases and 14,160 controls matched for age, gender, and date of index event. Naproxen therapy reduced the risk of MI as compared with other NANSAD (odds ratio, 0.79; 95% confidence interval, 0.63 to 0.99).

A prospective study using Tennessee Medicaid patients examined a cohort of 181,441 new NANSAD users who were age- and gender-matched to an equal number of nonuser controls (28). The study included patients 50 to 84 years of age with 532,634 person-years of follow-up. The primary end point was hospitalization for MI or death from CHD. Overall, the study found similar risks for MI among current naproxen users compared with nonusers. However, when directly compared with ibuprofen users, the risk of MI was lower with naproxen (odds ratio, 0.83; 95% confidence interval, 0.69 to 0.98). It was not clear if this difference was due to a protective naproxen effect or a detrimental effect of ibuprofen.

One additional observational study has examined whether NANSAD use after MI was associated with a protective effect similar to that of aspirin (29). Data were analyzed from 48,584 Medicare patients in the Cooperative Cardiovascular Project hospitalized for MI with no known contraindications to NSAID. At discharge, 1.5% of patients were prescribed NANSAD, 74.5% were prescribed aspirin, 4.3% received prescriptions for both drugs, and 19.6% received neither drug and served as controls. The primary outcome was mortality within one year of hospital discharge. Compared with controls, the hazard ratios were 0.77 (95% confidence interval, 0.65 to 0.90) for NANSAD, 0.81 (95% confidence interval, 0.77 to 0.86) for aspirin, and 0.78 (95% confidence interval, 0.69 to 0.88) for combined
therapy. Overall, the cardioprotective effects of NANSAD and aspirin were similar with no additional benefit associated with combined therapy. Interestingly, naproxen accounted for only 13% of the NANSAD prescriptions. Differences between the various NANSAD were not evaluated, and the COX-2 inhibitors were not available. This is the first study reporting similar survival benefits after MI for NANSAD and aspirin. However, due to the retrospective design, these findings should be interpreted with caution.

ROLE OF COX-2 IN CARDIOVASCULAR FUNCTION

It has been suggested that COX-2 inhibitors may increase cardiovascular risk by promoting thrombosis. This hypothesis is not without merit because these agents lack antiplatelet effects (due to minimal COX-1 inhibition) and decrease prostacyclin (PGI₂) production, which has vasodilating, antiaggregatory, and antiproliferative properties (17,30). Thus, it has been suggested that the increased cardiovascular risk may result from unopposed thromboxane A₂ actions. In addition, various experimental models have suggested a cardioprotective role for the COX-2 isozyme that might be blocked by COX-2 inhibitors. Cyclooxygenase-2 is expressed at low levels by endothelial cells under static conditions but induced under conditions of laminar shear stress (31). These findings suggest that decreased prostacyclin secondary to COX-2 deficiency may increase the risk of focal atherogenesis at sites of vascular bifurcation. It has also been shown in conscious rabbits that COX-2 mediates cardioprotective effects during the late phase of ischemic preconditioning (32). However, administration of COX-2 inhibitors to the rabbits 24 h after ischemic preconditioning eliminates the cardioprotective effect of late ischemic preconditioning against myocardial stunning and MI. These and subsequent studies have demonstrated that upregulation of COX-2 plays a key role in cardioprotection, which may be mediated through PGE₂ and PGI₂ (32,33). Other studies using a canine coronary thrombosis model found that the administration of a COX-2 inhibitor abolishes the increased time to arterial occlusion produced by aspirin (34). Studies in a rat model demonstrated that the chemotherapy drug doxorubicin induces COX-2 activity in neonatal myocytes, which, in turn, limits the drug-induced cardiotoxicity. However, administration of COX-2 inhibitors attenuated this cardioprotective effect (35). In addition, a recent study in mice suggests that COX-2 inhibitors may increase vascular response to injury as well as thromboxane A₂ synthesis and platelet activation (36). The study used genetically engineered mice that either overexpress or lacked receptors for thromboxane A₂ and/or prostacyclin. In mice lacking the prostacyclin receptor, mechanical injury to carotid vessels led to obstruction. In this scenario, which mimics selective COX-2 inhibition, thromboxane A₂ was overproduced by both platelets and the injured vessel wall. In contrast, the obstructive response was muted in mice who lacked either the thromboxane A₂ receptor or both receptors.

LIMITATIONS OF THE CURRENT EVIDENCE

Evidence for increased cardiovascular risk with COX-2 inhibitors is inconclusive. None of the randomized trials were powered to examine cardiovascular outcomes, thus introducing the possibility of bias. Baseline cardiovascular risk varied significantly among the studies. The VIGOR study was conducted in patients with rheumatoid arthritis, a disease associated with significant cardiovascular risks (37). Conversely, CLASS included primarily patients with osteoarthritis, which is not associated with increased cardiovascular risk. The secondary analyses of the VIGOR and CLASS data by Mukherjee et al. (6) have also raised methodological concerns (38) regarding the validity of comparing crude MI rates from high-risk rheumatoid arthritis patients to a placebo group constructed from low-risk patients in primary prevention trials. The analyses of 23 rofecoxib clinical trials with a mixed patient population including rheumatoid arthritis, osteoarthritis, Alzheimer’s disease, and back pain failed to show an increased thrombotic risk (22). Additionally, the analyses of 5,435 participants in the rofecoxib osteoarthritis development program found no difference in cardiovascular events between rofecoxib, comparator nonselective NSAID, and placebo (21). Therefore, while it is possible that COX-2 inhibitors increase cardiovascular risk, the data are inconsistent, and it is likely that baseline patient risk plays a significant role.

Furthermore, it is not yet clear whether there are differences between COX-2 inhibitors because studies of celecoxib have not reported increased cardiovascular events (18). As previously noted, the COX-2 selectivity of celecoxib is less than that of rofecoxib. At daily doses of 400 mg twice daily (similar to CLASS doses), celecoxib has been shown to produce some COX-1 inhibition and a degree of selectivity similar to the nonselective agent diclofenac (39). Additional studies are needed to examine the impact of COX selectivity.

The hypothesis that a cardioprotective effect of naproxen may explain the VIGOR findings is plausible but inconclusive. Naproxen has been shown to be a stronger inhibitor of COX-1 than either ibuprofen or diclofenac (40). Inhibition of thromboxane by 95% and platelet aggregation by 88% has been shown with naproxen during a typical dosing interval. In addition, diclofenac causes 94% inhibition of COX-2 compared with 71% with naproxen (40). To date, no prospective clinical trials have evaluated naproxen for cardioprotection. Interpretations from observational studies are subject to the many limitations inherent to this design including the inability to prove causation. Although the data suggest that naproxen may be advantageous over other nonselective NANSAD, the degree of cardioprotection is not of the magnitude of aspirin (41). Finally, because COX-2 inhibitors were not included in the naproxen studies, the findings do not provide a definitive explanation for the increased cardiovascular risk in the rofecoxib studies.

Additionally, the cardiovascular impact of combined
therapy with aspirin remains unclear. None of the studies were adequately powered to specifically address this question, and nonprescription or unreported use of aspirin could not be controlled. Recently, improved endothelial function was reported with celecoxib in CHD patients previously stabilized on aspirin and statins (42). In crossover fashion, 14 males received celecoxib 200 mg twice daily or placebo for two weeks. As measured by flow-mediated brachial artery vasodilation, celecoxib significantly improved endothelium-dependent vasodilation compared with placebo. Additionally, both C-reactive protein and oxidized low-density lipoprotein were significantly lower with celecoxib. This is the first study suggesting that a COX-2 inhibitor might improve endothelial function and reduce low-grade inflammation and oxidative stress in patients with severe CHD. Additionally, a recent pilot study found that addition of the COX-2 inhibitor meloxicam to low-dose aspirin and heparin improved clinical outcomes after non-ST-segment elevation acute coronary syndromes (43). These small studies suggest that combined aspirin and COX-2 inhibition could have beneficial cardiovascular effects.

Additional prospective trials are needed to assess the cardiovascular risks of NSAIDs. The upcoming gastrointestinal safety trial for lumiracoxib will evaluate cardiovascular events as a secondary end point and include patients taking low-dose aspirin for cardioprotection. Ibuprofen and naproxen will serve as comparators in this 12-month trial, which should address many of the ongoing concerns. However, because all of the issues that have been raised cannot be examined in clinical trials for various practical and ethical reasons, there is also a need for long-term postmarketing studies and well-designed epidemiological studies. In particular, further study is needed to examine the impact of combined therapy with aspirin and other NSAIDs on bleeding.

CONCLUSIONS

Recent study findings have demonstrated that our present understanding of the impact of COX inhibition on cardiovascular risk is incomplete. Studies are needed to determine the comparative cardiovascular effects of various COX-2 inhibitors and the impact of baseline risk. Cardioprotective effects of naproxen and other nonselective NANSIAD should also be studied further but, in the absence of definitive data, these agents should not replace aspirin. Finally, the cardiovascular impact of various combinations of aspirin and other COX inhibitors requires further study.

References


38. Lipani J. The data are inconclusive and these drugs are needed. Cleve Clin J Med 2001;68:961–2.


