Nonsteroidal antiinflammatory drugs (NSAIDs) are some of the most commonly used drugs around the world. In the United States, an estimated 17 million individuals are utilizing these drugs daily.\(^1\) Approximately 60 million prescriptions for various forms of NSAIDs are written each year, the majority are for the elderly.\(^2\) These drugs have been shown to be effective in the treatment of acute and chronic painful and inflammatory musculoskeletal conditions. At least 20 different types of nonselective NSAIDs (NS-NSAIDs) are available in the United States, including aspirin and the various formulations of the nonacetylated salicylates and the nonsalicylate NSAIDs. Aspirin and 3 NS-NSAIDs are available as over-the-counter products. In addition, cyclooxygenase-2 (COX-2) selective inhibitors have become available; of the latter drug class, only celecoxib is on the market in the U.S.\(^3\)

Despite the inherently low incidence of NS-NSAID-induced adverse effects involving the gastrointestinal (GI) tract, the widespread use of NSAIDs and the recent issue regarding cardiovascular (CV) thromboembolic events with all NSAIDs have resulted in any incident adverse event being considered a significantly larger problem. Increased use of NSAIDs in an aging population will increase the number of adverse events related to NSAID use. It has been estimated that 5% to 7% of hospital admissions are related to adverse drug effects, with 30% of these hospitalizations resulting from GI, nervous system, renal, or allergic effects of aspirin or non-aspirin NS-NSAIDs.\(^4\)

In considering the choice of drug, it is important for patients and their physicians to remember that all drugs are associated with some risk. That risk may range from a rather unimportant rash to the risk of death, depending on the therapy. The decision to treat with any therapy has to weigh the potential risk against the potential benefit. The NSAIDs are palliative drugs. There is no evidence that they alter the natural history of a disease, such as osteoarthritis (OA) or rheumatoid arthritis (RA); however, pain also deserves treatment and inflammatory pain responds well to an NSAID. With the use of NSAIDs, many different types of risk need consideration. The typical risks that are considered as related include ulcer and ulcer complications and the attendant risk of GI-related death. Other recently appreciated risks, such as those associated with acute myocardial infarction, worsening hypertension, stroke, or sudden CV-related death also need to be considered. The risks for GI damage associated with the use of NS-NSAIDs has been somewhat mitigated by the availability of COX-2-selective inhibitors and by proton pump inhibitors. Thus, in considering the risk and benefit of an NSAID, the risks regarding the GI tract and the cardiorenal system have to be weighed as competing risks.

Relative Benefit

Osteoarthritis (OA), generally considered a disease of the elderly, affects 16 to 20 million Americans.\(^5\) The prevalence of OA increases with age; 80% of Americans older than 65 years of age have radiographic evidence of OA, and, by age 80 years, the majority show clinical signs of the disease.\(^6\) The currently available NSAIDs are effective in reducing the pain and inflammation due to OA. Half of all NSAID prescriptions in the elderly are for managing the symptoms of OA.\(^7\) Because of the GI risks and potential CV thromboembolic events associated with NSAIDs, particularly in the elderly, it is unclear whether the degree of pain relief management produced by this drug class is superior to that of simple analgesics, such as acetaminophen. This impor-
tant issue was addressed in two double-blind, randomized, controlled trials by Pincus and colleagues. The studies demonstrated that pain management with NSAIDs was superior to that with simple analgesics but was associated with more GI distress. In these unique studies, the patients were asked to determine which therapy they preferred, the NSAID or acetaminophen. The patients in both crossover studies consistently preferred the beneficial effects of the NSAID, despite the increased risk of GI adverse events as compared with the effect of acetaminophen. These findings were also demonstrated in a separate study by Case and coworkers. Although NSAIDs do not seem to affect the pathophysiology of joint destruction in OA, such as reducing osteophyte formation, protecting cartilage, or preventing mechanical malalignment, NSAIDs reduce pain, decrease gel phenomenon, and improve function in patients with OA. It is unclear whether this analgesic benefit is due to their antiinflammatory or only analgesic effects.

It is important to balance the positive effects against the potential adverse effects of NSAIDs, particularly in the elderly. Despite the demonstrated superiority of NSAIDs versus simple analgesics in terms of efficacy, some patients do benefit from the simple analgesics alone and it is advisable to consult current guidelines for treating patients with OA. These guidelines typically recommend initiating therapy with the lowest dose and starting with acetaminophen, unless the patient has already failed that strategy.

Patients with other diseases, including RA, ankylosing spondylitis, and other forms of inflammatory arthritis, as well as chronic and acute pain, often use NS-NSAIDs or COX-2-selective inhibitors. The side effect profile and risk-benefit profiles are similar except in children. Children do not have the same increased risk for GI adverse events when treated with NS-NSAIDs as do adults, and there are not yet any data on the CV risk of these drugs in children who use them chronically.

Relative Risk

Despite the benefits of NSAIDs for acute and chronic pain, one of the most clinically significant and well-characterized adverse effects are on GI mucosa, including esophagitis, esophageal stricture, gastritis, mucosal erosions, and bleeding, as well as the development of peptic ulcer or its complications, including perforation, significant hemorrhage, obstruction, and death. In addition, there is increasing evidence for adverse effects on the small and large bowel mucosa, as well as evidence that these drugs may induce stricture formation that may, in turn, precipitate small or large bowel obstruction, a situation that can be difficult to detect on contrast radiographic studies. An autopsy study of 713 patients showed that small bowel ulceration, defined as ulcers greater than 3 mm in diameter, was observed in 8.4% of patients exposed to NS-NSAIDs, compared with 0.6% of nonusers of NSAIDs. Ulcerations of the stomach and duodenum were observed in 22% of NS-NSAID users, compared with only 12% of nonusers. Furthermore, there has been evidence that NS-NSAIDs may induce dysfunction in gut permeability.

Endoscopic studies have demonstrated that NS-NSAIDs classically produce shallow erosions or submucosal hemorrhages that can occur at any site in the alimentary tract, but are observed more commonly in the stomach near the prepyloric area and the antrum. Typically, many of these GI lesions are asymptomatic, which makes prevalence data very difficult to determine. Unfortunately, it is not known how many of these lesions spontaneously heal or which may progress to develop ulceration and then extend to frank perforation, obstruction of the viscous membrane, or serious GI hemorrhage, and even subsequent death.

For patients with RA, the true magnitude of risk associated with NS-NSAIDs in inducing GI adverse events is controversial; however, the U.S. Food and Drug Administration (FDA) has published a general risk of 2% to 4% per year for NS-NSAID-induced gastroduodenal ulcer, its ensuing complications, or both. In general, the relative hazard ratio has been estimated from several studies between 4.0 and 5.0 for the development of gastric ulcer; 1.1 and 1.6 for the development of duodenal ulcer; and 4.5 to 5.0 for the development of clinically significant gastric ulcer with hemorrhage, perforation, or death.

Fries and associates, in a univariate analysis of 2400 patients with RA, demonstrated a hazard ratio for hospitalization due to adverse GI effects as seven-fold that of patients not treated with NSAIDs. The population at greatest risk for peptic ulceration, with or without complications or death, was the elderly and those with a history of peptic ulceration.

**Table 1** Risk Factors for Nonselective-Nonsteroidal Antiinflammatory Drug-Induced GI Adverse Effects

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased age</td>
<td>older than 65 years</td>
</tr>
<tr>
<td>History of peptic ulcer disease or bleeding from the GI tract</td>
<td>use of antiulcer therapy for any reason</td>
</tr>
<tr>
<td>Concomitant use of glucocorticoids</td>
<td>particularly in patients with RA</td>
</tr>
<tr>
<td>Comorbid illness</td>
<td>such as significant CV disease</td>
</tr>
<tr>
<td>Patients with more extensive or severe rheumatoid arthritis</td>
<td>22,32,33</td>
</tr>
<tr>
<td>Increasing dose of specific and singular NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Concomitant use of glucocorticoids</td>
<td>which may increase the risk for peptic ulcer disease as much as 4-fold</td>
</tr>
<tr>
<td>Combinations of NSAIDs</td>
<td>increase the risk for patients sustaining a significant GI adverse effect</td>
</tr>
</tbody>
</table>
Although the risk for healthy patients may be smaller, NS-NSAID-related GI side effects were responsible for approximately 2000 deaths and 20,000 hospital admissions in the RA group per year. A meta-analysis of pooled data showed a relative risk for adverse GI effects due to NS-NSAIDs that were three-fold that of the non-NSAID population.24 Bleeding in the elderly is often silent and presents an increased risk for emergency surgical intervention for either bleeding or peptic ulcer with associated increased mortality. While there are theoretical reasons not to use anticoagulants when taking NSAIDs to decrease the risk of bleeding if an ulcer develops, no data demonstrate that anticoagulants cause ulcers. The presence of Helicobacter pylori infection does not appear to increase the risk for peptic ulcer disease in NS-NSAID users.36,37 The risk factors for an NSAID induced GI event are noted in Table 1.

Another clinically important but significantly less well characterized adverse event is the risk for stroke, acute myocardial infarction, and sudden cardiac death, recognized in some patients treated with either selective or nonselective NSAIDs. It appears that this risk is somewhat related to the risk for hypertension; it is not entirely correlated with the half-life of the drug, and it does not appear that significant inhibition of COX-1 activity totally mitigates the risk. Less frequent adverse effects include changes in the central nervous system, peripheral nerves, skin, and pulmonary or hepatotoxic reactions. Because many of the important toxic effects of these drugs are secondary to their primary mode of action, an understanding of the indications, mechanisms of action, and causes of these potential adverse effects is important, as is the identification of high-risk groups for the purposes of appropriate monitoring, treatment, and prophylaxis in order to allow for effective use and to minimize all NSAID-induced complications.

Minimizing Nonselective-Nonsteroidal Antiinflammatory Drug-Related GI Adverse Effects

In the attempt to limit GI adverse effects of NSAIDs, different preparations and routes of administration have been tried; however, ulcers have occurred with enteric-coated preparations, parenteral administration, suppositories, and oral ingestion of a prodrug formulation, such as sulindac. Nonacetylated salicylates appear to be better tolerated than other NS-NSAIDs. The onset of dyspepsia remains poorly understood and does not appear to be primarily mediated by prostaglandin metabolism.

The nonacetylated salicylates, including salsalate, magnesium choline trisalicylate, and diflunisal, as well as several of the nonsalicylate NSAIDs, such as low-dose etodolac, low-dose ibuprofen, and nabumetone, are reportedly less toxic to the GI mucosa than the other NS-NSAIDs.21,34,35 It has been suggested that etodolac, nabumetone, and meloxicam, because of their lower doses, can exhibit “selective” or “preferential” COX-2 inhibitory effects, leading to reduced effects on COX-1 activity.34,35 Because it is not a weak organic acid, at the pH of the stomach, nabumetone is not highly lipophilic and, thus, does not penetrate the mucosal barrier, which is rapidly penetrated by all other available NS-NSAIDs in the presence of stomach acid. The “ion-trapping” that is observed with all of the available NS-NSAIDs except nabumetone is probably an important factor in the local superficial damage induced by the NS-NSAIDs and is not modulated at all by COX activity. By penetrating the gastric mucous barrier (the thick hydrophobic mucous layer along the stomach lining), the weakly acidic, unionized NS-NSAIDs result in oxidative uncoupling of cellular metabolism, the outcome of which is cell death and local tissue injury.

These breaks in the mucosa may heal or, in the presence of gastric acid, become erosions; with more acid and the right conditions, these same lesions can develop into significant ulcers. Other relatively safer drugs, such as nabumetone, low-dose ibuprofen (< 1600 mg/24 hours), and etodolac, are usually listed together with similar effects. However, all of the presently available NS-NSAIDs, when used at high enough antiinflammatory doses, may induce significant GI mucosal damage. NSAIDs with prominent enterohepatic circulation and significantly prolonged half-lives, such as sulindac and piroxicam, have been linked to increased GI toxicity, due to increased reexposure of the gastric and duodenal mucosa to bile, which contains the active moiety of the drug.

Justification for the Development of COX-2 Selective Inhibitors

Nonsteroidal antiinflammatory drugs inhibit the activity of cyclooxygenase, the enzyme that catalyzes the synthesis of cyclic endoperoxides from arachidonic acid to form proinflammatory and other forms of prostaglandins.19,20 Prostaglandins can produce both positive and negative effects depending on their site of production. When synthesized at sites of inflammation, prostaglandins play a role in increasing local inflammation and enhancing pain sensation. They have also been shown to be important in the modulation of pain in the spinal cord and brain. In contrast, in the gastric mucosa, prostaglandins play a major role in protecting and promoting adequate blood flow to the gastric mucosa.36-41 In the kidney, prostaglandins act to modulate intrarenal plasma flow and electrolyte balance.19,20

The different physiologic outcomes of inhibiting cyclooxygenase and the differences in prostaglandin action are due to the existence of two isoenzymes of cyclooxygenase, COX-1 and COX-2.42-47 At the sites of inflammation, COX-2 isoenzymes predominate, and in the gastric mucosa and kidneys, COX-1 isoenzymes predominate. The ability to inhibit COX-1 and 2 varies considerably among the different NS-NSAIDs. Most do so in a nonselective fashion; the net outcome is a combined positive and negative prostaglandin effect, which in the gastric mucosa, for example, presents
as gastric ulcer.\textsuperscript{38,48,49}

The development of a targeted inhibitor of COX-2 isoenzyme (thus, a COX-1-sparing drug) allows inhibition of the proinflammatory and pain-causing prostaglandins without affecting the COX-1 and the GI-protective prostaglandin and is, thus, associated with less risk for GI damage. COX-2-targeted agents have been shown to decrease pain and inflammation in patients with OA and RA, while having less discernible effect on the gastroduodenal mucosa by endoscopic evaluation.\textsuperscript{40-55} However, although COX-2 is upregulated in inflammation, its activity is also upregulated in healing damaged tissue; thus, inhibition of COX-2 activity may delay healing in certain circumstances. How important this is clinically remains controversial.

**Clinical Benefits COX-2 Selective Inhibitors**

From a clinical perspective, the effectiveness of COX-2 selective inhibitors, in terms of antiinflammatory activity and pain relief, are comparable to those effects of NS-NSAIDs, at least in the studies that have been used as pivotal for approval. The first of the COX-2 selective inhibitors, celecoxib, was approved based on the results of five clinical trials involving more than 5200 patients with OA or RA, in which its efficacy and toxicity were compared to those of NS-NSAIDs and placebo.\textsuperscript{56,59}

The COX-2 selective (COX-1-sparing) inhibitors, such as celecoxib, are associated with reduced GI mucosal damage, as demonstrated in several trials. For example, the surveillance endoscopy trial involved 688 patients, with RA patients randomly assigned to various doses of either celecoxib, naproxen, or placebo for 12 weeks.\textsuperscript{56} All doses of celecoxib and naproxen improved signs and symptoms of arthritis compared with placebo. Similar results were found in a second study of 655 patients with RA that compared the efficacy and GI toxicity of celecoxib versus those of diclofenac.\textsuperscript{57} Other studies support the evidence that the COX-2 selective drugs have comparable efficacy to the NS-NSAIDs in patients with OA.\textsuperscript{58,60,61} RA,\textsuperscript{62,63} and ankylosing spondylitis.\textsuperscript{64}

The incidence of endoscopically determined gastroduodenal ulcers among patients taking celecoxib was similar to that with placebo (approximately 4%) and was significantly lower than that observed with naproxen (26%). Both valdecoxib and rofecoxib provide similar benefits.

The Celecoxib Long-term Arthritis Safety Study (CLASS) trial compared three treatments: celecoxib 400 mg twice a day, diclofenac 75 mg twice a day, and ibuprofen 800 mg 3 times a day.\textsuperscript{55,56} Total exposure to celecoxib was 2320 patient-years (mean patient exposure duration was 9 months). Seventy-two percent of the patients had OA and 28% had RA—21% were considered by their healthcare provider to be at high risk for CV events and were taking low-dose aspirin. The primary outcome measures for this study were complications of ulcers, limited to perforation, obstruction, bleeding, and death. This resultant outcome was not different among the three therapies; thus, the study failed in this regard. However, the secondary outcome of symptomatic ulcers along with the complications was statistically significantly better in the celecoxib-treated patients as compared with the combined group treated with ibuprofen or diclofenac at 1 year. This has subsequently been reflected in changed FDA product labeling acknowledging this benefit of celecoxib.

In a separate trial, the effect of rofecoxib on adverse clinical GI events (gastroduodenal perforation or obstruction, upper GI bleeding, and symptomatic gastroduodenal ulcers) was evaluated in 8076 RA patients, randomly assigned to rofecoxib or naproxen.\textsuperscript{65} The total exposure to rofecoxib was approximately 3947 patient-years versus 3078 patient-years of exposure to naproxen. The mean patient exposure was 9 months. Results demonstrated significantly fewer GI adverse events with rofecoxib as compared with naproxen (2.1 versus 4.5 per 100 patient-years; relative risk, 0.5; 95% confidence interval, 0.3 to 0.6). Both valdecoxib in its clinical exposure and celecoxib in ankylosing spondylitis show similar results.\textsuperscript{63,64} Comparable outcomes have been observed with lumericoxib (400 mg/day); the latter study demonstrating a decrease in symptomatic ulcers and associated complications by more than 75% in 7000 patient-years of exposure, compared with naproxen 500 mg twice daily or ibuprofen 2400 mg/day.\textsuperscript{65} Furthermore, a 138-week study in OA patients demonstrated comparable efficacy and safety with naproxen.\textsuperscript{66} Preliminary evidence also suggests overall reduced GI complications with the COX-2 selective inhibitors compared with NS-NSAIDs, even with concomitant use of proton pump inhibitors.\textsuperscript{67,69}

Collectively, these studies demonstrate significantly reduced GI complications with COX-2 selective inhibitors, compared with NS-NSAIDs, and a reduction in potential fatalities resulting from GI complications.

**Side Effects of COX-2 Selective Inhibitors**

As with all therapies, side effects with cyclooxygenase inhibitors can be expected, and lessons have been learned from the several nonprostaglandin-mediated mechanisms of action of NS-NSAIDs, demonstrated in experimental models. For example, NS-NSAIDs have been shown to reduce the expression of L-selectin, thus, affecting a critical step in the migration of granulocytes to sites of inflammation.\textsuperscript{70} In vitro NS-NSAIDs inhibit inducible nitric acid synthetase, which has been associated with increasing inflammation.\textsuperscript{71,72} The clinical significance of these nonprostaglandin-mediated processes in inflammation is unknown. It is also unknown whether the COX-2 selective inhibitors will demonstrate these same effects although studies show that agents in these drug classes may have different effects from each other, possibly unrelated to prostaglandin inhibition.\textsuperscript{73,75} These include different effects on cellular membranes and on brachial artery blood flow.

Hence, there appears to be comparable efficacy between
the COX-2 selective inhibitors and the NS-NSAIDs, with the recognition that some patients may respond to one therapy and not another. The reasons for these differences in response remain unclear. In addition, it is important to balance the benefits of these agents against their overall safety record on the basis of current knowledge and the evidence that may emerge from the ongoing studies.

**CV Risk with Both Selective and Nonselective NSAIDs: Evidence From Clinical Trials**

There is evidence regarding a possible risk for CV thromboembolic events with COX-2 selective inhibitors as well as the NS-NSAIDs. This presents an important clinical dilemma regarding the relative benefit of a gastroprotective effect of COX-2 inhibitors versus the relative risk for CV thromboembolic events and related risk for death from both groups of therapeutics, due to a CV event or a complicated GI adverse event. Currently, a methodology to assess the magnitude of these competing risks has yet to be developed.

The issue of clinically important risk for CV thromboembolic events began early in the study of these drugs. The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial was designed to investigate the GI safety of rofecoxib in patients with RA. Patients taking low-dose aspirin were excluded. The total exposure to rofecoxib was approximately 3947 patient-years versus 3078 patient-years of exposure to naproxen. The mean patient exposure was 9 months. However, the study revealed that after 80 days of treatment and continuing throughout the trial, significantly more thromboembolic CV events occurred in patients receiving rofecoxib 50 mg daily, compared with those receiving naproxen 500 mg twice daily; the incidence of MI was 0.5% versus 0.1%, respectively. In contrast, in the CLASS trial, no differences in CV or cerebrovascular events were observed between the celecoxib (400 mg twice a day) and the NS-NSAID treatment groups (diclofenac, 75 mg twice a day, with 1081 patient-years of exposure, and ibuprofen, 800 mg three times a day, with 1123 years of patient exposure) regardless of aspirin use. The reason for these results with celecoxib remains unclear; however, a plausible explanation is the fewer patient-years of exposure in CLASS compared to VIGOR, as well as the lower risk for thromboembolic CV events in the CLASS patient population, because most patients had OA. It is also possible that the results seen with rofecoxib are unique to this compound and unrelated directly to its COX-1-sparing effects.

It is interesting to question why more patients receiving rofecoxib experienced more myocardial infarction (MI) than those receiving naproxen in the VIGOR trial; a trial that evaluated GI safety of rofecoxib compared with naproxen and in which the CV risk was a secondary outcome measure. Several hypotheses have been presented as plausible explanations. For example, it has been suggested that rofecoxib induced a prothrombotic state by inhibiting the vasodilator effects of endothelial prostaglandin I\(_2\) without affecting thromboxane A\(_2\) (a product of COX-1 catalysis), resulting in an unbalanced prothrombotic state in patients at risk. Naproxen, which has a long half-life, may have sufficiently inhibited platelet thromboxane A\(_2\) synthesis by COX-1 as to become cardioprotective in some patients. It is also possible that these findings are a combination of effects yet to be resolved.

These observations prompted multiple epidemiologic studies and reanalyses of the new drug application and postmarketing study databases for evidence of increased CV risk with COX-2 selective agents. Meta-analyses of the new drug application databases did not reveal increased risk, although the trials were typically short, had multiple comparator NSAIDs (also short exposure), had no placebo group, and were conducted in more patients with OA than RA, using COX-2 agents at recommended doses rather than those used in CLASS and VIGOR studies. In addition, the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) demonstrated no statistically significant increased risk for CV events with the selective COX-2 inhibitor lumiracoxib. Although numerically higher than in the group receiving naproxen, the overall incidence of these events was quite low.

In 2001-2002, the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) trial took place, involving more than 30,000 patients over 3 years. The purpose was to study the risk for adverse CV outcomes in patients treated with etoricoxib at 60 mg and 90 mg daily compared with diclofenac 75 mg twice daily. On completion of the study in 2006, the data demonstrated no significant difference in rates of acute MI, sudden cardiac death, stroke, or other forms of thrombosis between the treatment groups. However, there was a significant increase in the number of patients receiving etoricoxib, compared with diclofenac, who withdrew from the trial due to congestive heart failure and worsening hypertension, although diclofenac was associated with worse GI tolerability and hepatotoxic reactions, compared with etoricoxib.

**CV Risk with both Selective and Nonselective NSAID Inhibitors: Evidence From Placebo-Controlled Trials**

With the approval of celecoxib, 400 mg twice a day, for the treatment of familial adenomatous polyposis, long-term studies were initiated and designed to compare either rofecoxib, 25 mg daily (APPROVe, Adenomatous Polyp Prevention on Vioxx Trial), or celecoxib, 200 mg to 400 mg daily, versus placebo for prevention of subsequent polyp formation. Celecoxib has also been studied in patients with Alzheimer’s disease. To date, long-term outcome trials have shown no risk for CV events with celecoxib at pain and arthritis doses, even in Alzheimer’s patients who, because of their age, were at a higher risk for a CV event. However, in two studies in the colonic polyp series, a 2.5- to 3-fold
increased relative risk for CV thromboembolic events was demonstrated with a 400 mg twice-daily dosing celecoxib schedule compared with placebo, whereas a once-daily dosing schedule or 200 mg twice-daily dosing demonstrated no increased risk compared with placebo.85,86

In patients at extremely high risk for CV events (specifically, those treated almost immediately after coronary artery bypass graft surgery), studies with paracoxib, an IV (intravenous) form of valdecoxib, revealed that a high dose was associated with an increased risk for myocardial infarction, stroke, and sudden death.89 However, due to the variability of the experimental design, it is difficult to arrive at a definite conclusion regarding the true CV risk for paracoxib in this patient group. On the basis of the findings, it is reasonable to suggest that IV COX-2 inhibitors (both NS-NSAIDs and COX-2 selective inhibitors, because both classes of drugs inhibit COX-2 activity) should not be used in patients at high risk for a CV event. Whether it is appropriate to extrapolate the effects of paracoxib to valdecoxib, often used chronically and at much lower doses in diseases such as OA and RA, is unknown.

**Epidemiologic Studies of Relative Risk for CV Events**

The value of studies attempting to establish the true risk for CV events with COX-2 inhibitors is limited, because the patients in the studies were generally not chronic users of these drugs. Thus, pharmacoepidemiologic trials are important to evaluate these possible outcomes. Initial studies by Rahme and colleagues90 and Solomon and coworkers91 failed to show differences in risk for CV events with rofecoxib and suggested that this was possibly due to the protective effects of naproxen.91 However, other epidemiologic studies failed to show a protective effect for naproxen or other NS-NSAIDs.76

Two subsequent large observational cohort studies found that doses of rofecoxib greater than 25 mg daily were associated with increased risk for CV events. Ray and associates82 studied the Tennessee Medicaid database and found an odds ratio of 1.7 for acute MI with doses of rofecoxib greater than 25 mg daily, compared with ibuprofen. This risk was observed specifically in new users, i.e., patients taking rofecoxib for less than 90 days. Solomon and colleagues93 analyzed a Medicare database from New Jersey and Pennsylvania and identified an increased relative risk for acute MI with rofecoxib doses greater than 25 mg daily, compared with celecoxib and traditional NSAIDs, again over the first 90 days of use, but not thereafter. A third cohort study, a collaborative study by the FDA and Kaiser Permanente, examined CV outcomes in approximately 1.4 million patients receiving NS-NSAIDs or selective COX-2 inhibitors. Doses of rofecoxib greater than 25 mg/day were associated with a more than three-fold higher incidence of acute MI and sudden cardiac death, compared with NS-NSAIDs or other selective COX-2 inhibitors.94 There was, again, no risk observed with celecoxib. Of interest, in the Medicaid, Medicare, and Kaiser Permanente databases, the incidence of acute MI with celecoxib treatment was lower than that with the other agents,92-94 and in the Kaiser Permanente analysis,94 naproxen was associated with an increased risk for thromboembolic CV events (relative risk [RR], 1.18; 95% confidence interval [CI], 1.04-1.35; p = .01), as was indomethacin (RR, 1.33; 95% CI, 1.09-1.63; p = .005), both being NS-NSAIDs with COX-1 and COX-2 inhibitory effects. Other epidemiologic studies95,96 have further corroborated the increased risk for MI associated with higher doses of rofecoxib, as well as increased risk for more renovascular events and arrhythmias.

Furthermore, robust data sets from clinical trials and new drug application summaries of both celecoxib and rofecoxib demonstrate a dose-related effect of rofecoxib on increasing blood pressure and causing edema, not apparent with celecoxib at any dose. Therapeutic doses of both celecoxib and rofecoxib for the treatment of arthritis pain are associated with an approximate 1% to 3% incidence of hypertension and edema, not different from that observed with NS-NSAIDs. However, a dose response for increased hypertension and edema is particularly evident with rofecoxib at 50 mg daily.97-103

**Effect of Nonselective-Nonsteroidal Antiinflammatory Drugs and COX-2 Inhibitors on Blood Pressure**

Patients with treated hypertension may have elevated levels of angiotensin II and norepinephrine. These vasoconstrictors promote the release of vasoconstrictor prostaglandins from the kidney, which act locally to minimize the degree of renal ischemia.95 When this compensatory response is inhibited by an NSAID, the increase in renal and systemic vascular resistance can cause an elevation in blood pressure. This effect can generally be induced by any NS-NSAID (including over-the-counter ibuprofen), but may be less likely to occur with sulindac or low-dose aspirin, or as well with other types of analgesics, such as acetaminophen.95,96

Typically, the NS-NSAID or COX-2 selective induced blood pressure changes are small; in one meta-analysis,104 the mean increase in supine blood pressure was 5.0 mm Hg. The study also showed that NSAIDs antagonized the antihypertensive effect of beta blockers (blood pressure elevation, 6.2 mm Hg) more than vasodilators and diuretics. Piroxicam produced the most marked elevation in blood pressure (6.2 mm Hg), while sulindac and aspirin had the least hypertensive effect. The consequences of these modest increases in blood pressure in patients taking NSAIDs have not been specifically studied. However, a 5 to 6 mm Hg elevation in diastolic blood pressure over several years may be associated with a 67% increase in total stroke occurrence and a 15% increase in coronary heart disease.97

Several studies98,105-108 have investigated the blood pressure effects of NSAIDs and COX-2 inhibitors. In hyperten-
sive patients (treated with various antihypertensive drugs, including angiotensin-converting enzyme inhibitors) who have OA, both rofecoxib and celecoxib cause an increase in systolic and diastolic blood pressure, which is more pronounced with rofecoxib. The ambulatory blood pressure monitoring trial compared the effects of celecoxib 200 mg, rofecoxib 25 mg, and naproxen 500 mg twice a day in hypertensive diabetic patients with OA being treated for high blood pressure. At 6 weeks, there was a sustained increase in systolic blood pressure of approximately 4.2 mm Hg with rofecoxib, but no increase with naproxen or celecoxib.

Although there is no evidence that these increases in blood pressure are associated with short-term increases in risk for acute MIs, there is clear evidence that chronically sustained increases in blood pressure are associated with ischemic cardiac events and stroke.

Treatment with valdecoxib, previously approved for use at 10 mg/day and 20 mg/day, appears to be associated with a higher incidence of hypertension and edema at 40 mg/day and 80 mg/day. The new drug application database has not revealed an increased risk for thromboembolic CV events, although the studies surrounding valdecoxib involve a smaller number of patients and do not include a large outcomes study compared to CLASS or VIGOR. Studies including an IV formulation did demonstrate an increased relative risk for a CV adverse event after coronary bypass graft surgery.

**Differential Effects of NSAIDs**

Studies have demonstrated a clear difference in the “differential selectivity” of rofecoxib, celecoxib, lumericoxib, etoricoxib, and valdecoxib for inhibition of COX-2 versus COX-1 activity, although in vitro and ex vivo assays using different molecular targets may not accurately reflect in vivo effects. Regardless, each of these agents effectively and selectively inhibits COX-2 activity when used in approved therapeutic doses, and none affects in vivo platelet aggregation at any recommended dose.

Although the precise explanation for the differences in selectivity and pharmacologic action is unknown, it is reasonable to assume that they may be due to differences in the drugs’ molecular structures, pharmacokinetics, and pharmacodynamics. Celecoxib and valdecoxib are sulfonamides; celecoxib has a halogenated side chain. Rofecoxib is a sulfone with a halogen-containing ring structure. The half-life of rofecoxib is more than 17 hours, compared with approximately 11 hours for celecoxib and 8 hours for valdecoxib. Lumericoxib has a half-life of 7 hours, whereas etoricoxib has a half-life of 22 hours.

The impact of half-life and dosing was demonstrated in the study where celecoxib was administered once or twice daily. This investigation showed that, compared to effects with placebo, a 2.5-fold increase in relative risk for MI, stroke, and CV death was observed in patients receiving twice-daily celecoxib, while the relative risk for these events was not significantly different from that with placebo in patients receiving once-daily celecoxib.

Recently, it has been demonstrated that acetaminophen, at more than 15 days of dosing per month, increases the relative risk above 1.5 for acute MI, sudden cardiac death, and stroke, particularly in patients who smoked. This finding is interesting because acetaminophen, at the usual analgesic dose, does not inhibit either peripheral COX-1 or COX-2 activity. This raises an interesting question regarding confounding by indication. In the Kaiser Permanente data, indomethacin had an elevated relative risk for MI and sudden cardiac death. This drug is used predominantly in patients with gout and hyperuricemia; both conditions have recently been associated with an increased relative risk for MI. It is also known that pain is associated with increased rates of hypertension. This suggests the question, “Is it possible that some of the increased relative risk for acute MI, stroke, and sudden cardiac death is modulated not by effects on cyclooxygenase, but by the underlying clinical condition?”

**Combination Therapy with Either NSAIDs or COX-2 Inhibitors**

**Combination with Aspirin**

Another issue that may arise is concurrent therapy with aspirin and a nonsalicylate NSAID. The dosage of aspirin used to protect against CV disease is often quite low (e.g., 81 to 325 mg/day). Such patients may have an indication for NSAID use. None of the nonsalicylate NSAIDs has been evaluated for cardioprotective effects in large studies, and, therefore, they are not recommended as a substitute for aspirin therapy. Thus, low-dose aspirin should be continued in such patients, possibly increasing the risk for an untoward GI event.

The desirable antplatelet effects of aspirin may be attenuated by previous or ongoing administration of a nonselective NSAID, such as ibuprofen or naproxen. This interference has been demonstrated to affect in vitro platelet aggregation. The clinical relevance of this in vitro study is suggested by the following data sets.

In a post-hoc subgroup analysis of a clinical trial of aspirin versus placebo for the prevention of a first MI, regular but not intermittent use of an NSAID (including ibuprofen and other NSAIDs) abrogated much of the beneficial effect of aspirin. In contrast, neither regular nor intermittent use of NSAIDs affected the risk for first MI among those who received placebo rather than aspirin. In this analysis, selective COX-2 inhibitors and diclofenac were not considered separately from other NSAIDs. In a report of 7107 patients with known coronary heart disease (almost 90% of whom were taking aspirin), 32% died during a median of 3.3 years of follow-up. The hazard ratio for CV mortality in the 187 patients taking both aspirin and ibuprofen was significantly higher than that in patients taking aspirin alone (hazard ratio, 1.73; 95% CI, 1.05-2.84). Other data support this finding.
Increased frequency of use of NSAIDs (0, 1 to 3 times, or 4 or more times) concomitantly with aspirin was associated with a significant decrease in the benefit of aspirin (odds ratios, 0.78, 0.97, 2.0, respectively). Interference with the cardioprotective effect of aspirin was seen with use of ibuprofen but not naproxen.

Among patients with known coronary artery disease, prescribing both aspirin and ibuprofen may not have a significant impact on mortality. For example, in a retrospective study of 70,316 patients who received a prescription for aspirin following hospitalization for MI, 884 received a concomitant prescription for ibuprofen, and 2733 for another NSAID. After adjustment for other risk factors, there were no significant differences in death rates during the year after hospitalization among those for whom aspirin was either prescribed alone, in combination with ibuprofen, or with another NSAID. Because aspirin and COX-2 selective inhibitors compete for different binding sites, the combination of aspirin and COX-2 may be more preferable, in the right patient, than its combination with a NS-NSAID.\textsuperscript{115-118}

**Combination With Anticoagulants**
Concomitant use of anticoagulants and NS-NSAIDs is not strictly prohibited; however, anticoagulants may predispose a patient to an increased risk for hemorrhage if a mucosal break has been precipitated by an NS-NSAID.\textsuperscript{119} In addition, when NSAIDs and oral anticoagulants are taken concurrently, a clinically significant increase in international normalization ratio (INR) may occur in some patients. This was demonstrated in a cohort of 112 Dutch patients treated with acenocoumarol who received an NSAID (diclofenac, naproxen, or ibuprofen).\textsuperscript{119} Of these 112 patients, 12 (11%) had increases in INRs to more than 6. Thus, if an NSAID is used concomitantly with a warfarin-derivative anticoagulant, frequent monitoring for INR is necessary. Additionally, if the dose of either drug is changed, then careful follow-up is required. Because the COX-2 selective inhibitors have been shown to have no effect on platelet aggregation, at least within clinical doses, they appear to be the drugs of choice for those patients who require concomitant anticoagulation with warfarin and an NSAID.

**Conclusions**
Weighing the available evidence, it appears that, as with the nonselective NSAIDs, there are differences in the pharmacologic action of the selective COX-2 inhibitors, as well as differences in patient response to these agents. In terms of efficacy, COX-2 inhibitors appear comparable to NS-NSAIDs in several chronic and acute situations. In some patients, they have a better safety profile than NS-NSAIDs. In view of the risk for GI adverse events associated with NS-NSAIDs, this is particularly important and significant in older patients who may need chronic pain management.\textsuperscript{120,121} Despite the increased risk for CV thromboembolic events seen with COX-2 selective inhibitors, because similar risks are observed with the NS-NSAIDs, when the available evidence is taken together, an overall assessment is to continue to allow access to these drugs. However, only further study can allow a fuller understanding of the relative risks associated with NS-NSAIDs and COX-2 inhibitors.

NS-NSAIDs used in combination with proton pump inhibitors or other gastroprotective strategies may suffice in place of the COX-2 selective inhibitors in some patients.\textsuperscript{122-126} However, there are no long-term outcome trials studying the effects on traditional GI outcomes; several noted studies question the CV safety of the NS-NSAIDs, which have also not been studied extensively.

There are several differences among the COX-2 selective inhibitors. For example, rofecoxib has demonstrated a dose-related risk for increased hypertension and edema as well as a risk for CV complications. Celecoxib does not appear to cause increased risk for hypertension or edema over a broad range of dosages (200 to 800 mg/day) that is dissimilar from the event rate with NS-NSAID comparators (1% to 3%), and the available data show a variable increased relative risk for acute thromboembolic CV events and little evidence at doses that are used to treat chronic arthritis patients, particularly at those doses used to treat most patients with OA. Valdecoxib appears to be associated with a dose-related increase in hypertension and edema at dosages of 40 to 80 mg/day—dosages higher than the 10 mg/day and 20 mg/day previously approved for chronic use. The limited accumulated evidence currently available does not reveal a significant increase in CV thromboembolism when valdecoxib is used chronically and at a low dose. However, there are no large outcome trials of risk for GI events or CV complications.

Certainly, larger outcome trials will be required to definitively arrive at a conclusion on the CV risk associated with COX-2 inhibitors; the current conclusion, based on available evidence, of an increased risk for CV events as a class effect of all selective COX-2 inhibitors appears premature. In an interesting, recent prescription billing record retrospective cohort study that compared the risk for CV events with the risk for a GI adverse event, Rahme and coworkers\textsuperscript{127} demonstrated that celecoxib and naproxen appear to be less risky in terms of a CV adverse event, while celecoxib and diclofenac appear least risky in terms of a GI adverse event. Drug choice should be driven by relative benefit and relative risk, and if the chosen drug leads to increased blood pressure or peripheral edema, then these adverse events should be treated aggressively if it is deemed important to continue the NSAID or COX-2 inhibitor.

As a recent advisory from the American Heart Association (AHA) suggests, the lowest possible dose of effective therapy should always be the initial choice.\textsuperscript{128} The comments from the AHA were based on accumulated evidence as well as two newer papers, including one by Gialason and associates, which demonstrated dose-response relationships with both nonselective NSAIDs (ibuprofen) and selective COX-2...
inhibitors (rofecoxib and celecoxib) as well as diclofenac for increased risk for reinfarction in patients who have recently sustained an MI prior to being treated with such analgesic and antiinflammatory therapy. The other paper demonstrated that, as in the females noted above, more than 15 days of therapy per month with acetyaminophen, NS-NSAIDs, or selective COX-2 inhibitors, may lead to increased relative risk for hypertension and CV thromboembolic events.

Although the AHA statement suggested that the COX-2 selective inhibitors should be the court of final therapeutic resort, there seem to be little data supporting that contention from the presented evidence, particularly when considering the chronic doses typically used in arthritis. As previously stated, there appears to be an increased risk for CV events with all of the available NSAIDs. Furthermore, Pincus and colleagues demonstrated that the use of an antiinflammatory drug is both more efficacious and preferable to the patients than the use of an analgesic alone in the treatment of patients with OA. Thus, the choice needs to be supported and acted upon considering all known risks and benefits, and if pharmacotherapy is required, then the lowest possible doses of whatever drug should be chosen first. Reassessment of positive effect and evaluation within weeks for worsening edema or hypertension is necessary, and if it is determined that continued NS-NSAID, acetyaminophen, or a selective COX-2 inhibitor should be chosen, then the edema or worsening hypertension, if present, should be treated appropriately and aggressively.

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