

Selective COX-2 Inhibitors and Cardiovascular Risk: Deciphering the Mystery

By Mimi Lo, Pharm.D.

In a move that stunned the nation, Merck announced the voluntary withdrawal of rofecoxib (Vioxx[®]) in the Fall of 2004 due to clinical evidence of an increased risk of adverse cardiovascular events.^{1,6} With worldwide rofecoxib sales totaling roughly \$2.5 billion, this move represented the largest dollar volume prescription drug withdrawal in history.¹ Information recently released to the FDA has also revealed an increase in cardiovascular events associated with celecoxib and valdecoxib use, which has hurled the selective COX-2 inhibitor drug class into a state of intense scrutiny and dampened enthusiasm for their use.^{2,3} Although the association of these popular drugs with cardiovascular risk came as a shock to the general public, the controversy over increased cardiovascular risk with COX-2 inhibitors has been brewing since the publication of the VIGOR trial in 2000.⁴ This pivotal trial, designed to compare gastrointestinal toxicity of rofecoxib and naproxen, spawned further inquiry when an unexpected five-fold increase of cardiovascular events in the rofecoxib group was reported.⁴ This article will review the pharmacology of NSAIDs, discuss the theoretical basis for a class effect of COX-2 inhibition on cardiovascular risk, and suggest a rational approach to the continued use of these agents.

There are two cyclooxygenase (COX) isoforms, COX-1 and COX-2, which are responsible for metabolizing arachidonic acid to various eicosanoids including thromboxane A₂, prostacyclin (PGI₂), and prostaglandin E₂ (PGE₂; see Figure 1). While the two isoforms possess a 66% homology in enzyme structure, their main functional differences are related to their expression in different tissues.⁵ COX-1 is expressed constitutively in platelets, vascular endothelial cells, gastric epithelial cells, and renal collection tubules and is involved in the regulation of physiologic processes such as platelet aggregation, stimulation of production and maintenance of protective gastric mucus, and homeostatic regulation of glomerular filtration in the kidney. Like COX-1, COX-2 is constitutively expressed in tissues such as the brain, kidney, endothelium, and spinal cord, but is also induced at sites of inflammation and injury by certain cytokines, endotoxins, and growth factors.⁶

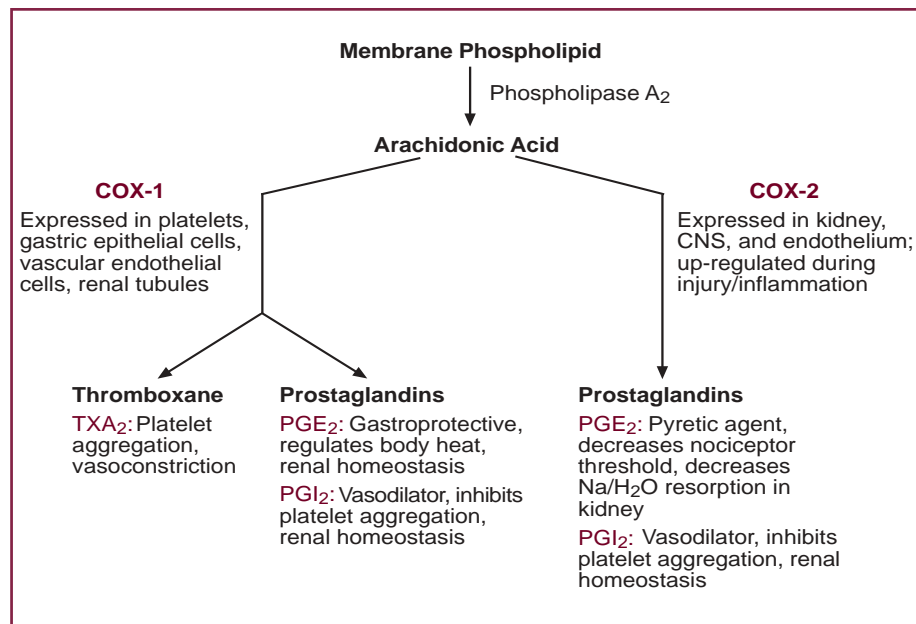
Evidence that COX-1 inhibition is the primary cause of injury to the gastric mucosa following NSAID use provided the impetus for the development of selective COX-2 inhibitors. It was hoped that selective COX-2 inhibition would offer the same anti-inflammatory efficacy with less GI toxicity. As seen in Figure 2, the ability of NSAIDs to selectively inhibit the two COX isoforms exists as a continuum.⁷⁻⁹ Agents such as ketorolac, aspirin, naproxen, and ibuprofen have a greater affinity for COX-1 inhibition, while agents such as etodolac, meloxicam and diclofenac are more selective towards COX-2. Although the 'coxib' drugs (celecoxib, rofecoxib, and valdecoxib) have been marketed as being uniquely COX-2 selective, this is not an accurate designation. Celecoxib, the first

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Figure 1: Role of Cyclooxygenase Isoforms in the Biosynthesis of Prostaglandins
(adapted from reference 10)



of the “selective” COX-2 inhibitors to be marketed, has a selectivity towards the COX-2 isoform roughly equivalent to that of the older traditional diclofenac (Voltaren^R). Although often overlooked, drugs such as meloxicam (Mobic^R) and etodolac (Lodine^R) are more selective inhibitors of COX-2 than celecoxib. Rofecoxib and newer agents like valdecoxib, etoricoxib, and lumiracoxib all have much higher affinities for COX-2 and relatively little affinity for COX-1 inhibition.⁷

Although the introduction of the more selective COX-2 inhibitors have been associated with a decrease in the incidence of GI bleeds in chronic anti-inflammatory drug users, multiple complex mechanisms are thought to contribute to the increase in cardiovascular risk. Together, the COX

NSAIDs can be ordered along a continuum according to their ability to selectively inhibit the COX-1 and COX-2 isoforms.

Although the ‘coxib’ drugs (celecoxib, rofecoxib, and valdecoxib) are labeled “COX-2 selective,” this is not a wholly accurate designation.

Celecoxib is roughly equivalent to diclofenac in COX-2 selectivity and meloxicam and etodolac are more COX-2 selective than celecoxib.

enzymes play an important role in cardiovascular homeostasis. As illustrated in Figure 1, COX-1 mediates the production of thromboxane A₂ (TXA₂), which promotes vasoconstriction and platelet aggregation.¹⁰ In platelets, COX-1 is the only isoform present. The COX-2 activity in macrovascular endothelium is up-regulated by laminar sheer stress and primarily produces prostacyclin (PGI₂), which promotes vasodilation, and inhibits platelet aggregation and adhesion.⁶ By the opposing action of these two isozymes, the vasculature is typically maintained in a balanced state between COX-2-mediated PGI₂ and COX-1-dependent TXA₂ production.⁶ Since non-selective NSAIDs inhibit both the formation of platelet thromboxane and endothelial prostacyclin, they are not thought to disrupt the normal hematologic equilibrium. On the other hand, it is hypothesized that selective COX-2 inhibitors disrupt the antithrombotic effects of PGI₂ and permit the unopposed pro-aggregatory action of TXA₂ on platelets.⁶ In this way, highly selective COX-2 inhibitors, such as rofecoxib or valdecoxib, are thought to be able to tip the balance to increase adverse cardiovascular thrombotic events in predisposed patients. Since celecoxib is the least COX-2 selective of the drugs in the ‘coxib’ class, it may inhibit the COX-1 isoform enough to overcome the pro-aggregatory effects of TXA₂, especially at supratherapeutic doses.⁸ Similarly, unbalanced COX inhibition can also uncouple the physiologic homeostasis between vasoconstrictive TXA₂ and vasodilatory PGI₂.⁶ Selective COX-2 inhibition of PGI₂ production may promote thromboxane-induced vasoconstriction and lead to vascular occlusion. However, the risk of COX-2 inhibitor-induced thrombosis in healthy patients should be small due to the presence of other endogenous substances, such as endothelium-derived nitric oxide, that protect against thrombotic and vasomotor imbalances.¹¹ Thus, patients with pre-existing cardiovascular disease are expected to be more susceptible to the adverse prothrombotic effects of selective COX-2 inhibition.

A linear relationship exists between blood pressure and cardiovascular/cerebrovascular disease; even a small change in blood pressure is known to impact the risk for cardiovascular events.¹² NSAID-induced deterioration of blood pressure control puts patients at risk for the development of cardiovascular events.^{13,14} In the kidney, the balance between production of PGE₂ and PGI₂ is largely responsible for renal vascular

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Multiple complex mechanisms, including the uncoupling of homeostasis between vasoconstrictive thromboxane A₂ and vasodilatory PGI₂ underlie the increase in cardiovascular risk demonstrated in association with selective COX-2 inhibition.

Several studies have confirmed a small but clinically significant increase in cardiovascular risk in patients treated with selective COX-2 inhibitors.

Ibuprofen is now known to be a poor choice in patients taking cardio-protective doses of aspirin. It is thought that the 3-dimensional configuration of the ibuprofen molecule mechanically prevents aspirin from acetylating platelets by blocking receptor access.

While clinical trials have confirmed a slight benefit for gastro-duodenal tolerability of the selective COX-2 inhibitors, the GI benefits are lost in patients taking aspirin.

homeostasis. PGE₂ plays a role in the regulation of intravascular volume by reducing sodium and water reabsorption in the collecting duct and thick ascending limb of the loop of Henle.¹³ PGI₂ serves to regulate renal vascular tone, glomerular filtration, and renin release. Preferential inhibition of PGE₂ production increases tubular sodium and water reabsorption while preferential inhibition of PGI₂ production allows for the unopposed action of vasoconstrictors on the vascular endothelium. In patients taking NSAIDs, the reduction in the production of these two prostaglandins can contribute to a deterioration in blood pressure control, especially in patients with renal insufficiency due to hypoperfusion, advanced age, or pre-existing disease.¹³ Studies have elucidated COX-2 as the primary isoform responsible for renal homeostasis, and therefore, it is thought that a selective COX-2 inhibitor-mediated increase in blood pressure could potentially contribute to the development of cardiovascular events in predisposed patients.¹⁴

Several studies have suggested a link between selective COX-2 inhibitors and an increase in cardiovascular risk^{4,15,16} (see Table I). The first evidence of this association was seen in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial.⁴ This study evaluated the GI safety of suprathreshold doses of rofecoxib vs. therapeutic doses of naproxen in patients with rheumatoid arthritis. Notably, patients with a history of coronary heart disease or aspirin/anticoagulant use were excluded from the study. Unexpectedly, a 5-fold difference in the incidence of acute MI was detected between the two treatment arms. In hindsight, it was determined that 4% of this study population qualified for low-dose aspirin for secondary prevention and that these patients accounted for 38% of the MIs reported. Further, 80% of the patients who had thrombotic events had one or more recognizable CV risk factors, and the incidence of cardiovascular events only differed between groups in the subset of patients judged to be candidates for aspirin. The results were suggestive of a prothrombotic effect of rofecoxib when used in patients already at risk for a cardiovascular event. Initially suggested to be an artifact of the comparison to naproxen (which has greater COX-1 selectivity and inhibits the production of TXA₂ and platelet aggregation to the same degree as aspirin⁹), the VIGOR trial findings were followed by the publication of pooled analyses which suffered from substantial methodological limitations but nevertheless served to cast doubt on the genuineness of the results.^{17,18} Then in

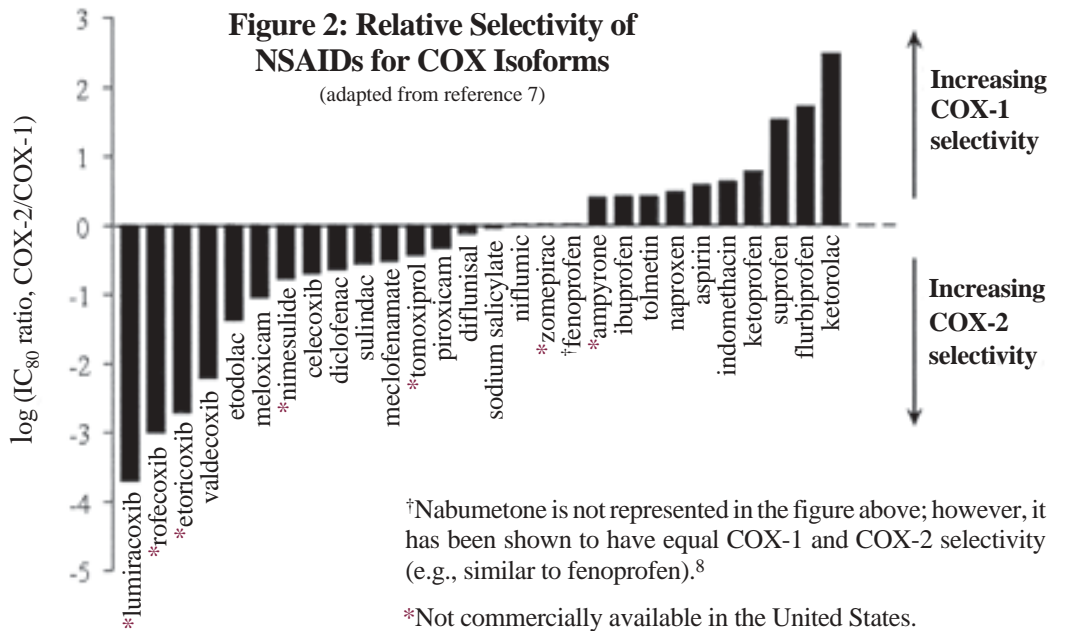


Table I: Randomized Controlled COX-2 Inhibitor Clinical Trials and Cardiovascular Outcomes

Study and patients		Regimen	Pre-existing Coronary Heart Disease/ Concurrent ASA	Cardiovascular Outcomes	Conclusions
Celecoxib	CLASS ²¹ N = 8,059 27% RA patients 73% OA patients	Celecoxib 400mg BID vs. Diclofenac 75mg BID vs. Ibuprofen 800mg TID	CHD not excluded. ASA allowed.	CV events at 9 months: <u>Overall</u> Celecoxib = 1.3% Diclofenac = 1.4% Ibuprofen = 1.1% <u>Patients not taking ASA</u> Celecoxib = 0.8% Diclofenac = 1.0% Ibuprofen = 0.4%	Overall, no statistically significant difference in CV events between groups. In non-ASA users, trend towards higher rates of CV events in celecoxib and diclofenac vs. ibuprofen group (NS).
	APC ² N = 2,026	Celecoxib 400mg QD 800mg QD vs. placebo	Not evaluated.	CV events: Celecoxib 400mg QD = 2.2% Celecoxib 800mg QD = 3% Placebo = 0.9%	Statistically significant increase in risk of cardiovascular events with either dose of celecoxib vs. placebo.
Lumiracoxib	TARGET ¹⁵ N= 18,244 OA patients 4,741 (lumiracoxib) vs. 4,730 (naproxen) and 4,376 (lumiracoxib) vs. 4,397 (ibuprofen)	Lumiracoxib 400mg QD vs. Naproxen 500mg BID Lumiracoxib 400mg QD vs. Ibuprofen 800mg TID	CHD excluded. ASA allowed.	All CV events: Lumiracoxib 0.65% vs. NSAIDs 0.55% (NS) CV event rate/100 patient years (non-ASA users): Lumiracoxib 0.80 vs. naproxen 0.53 (P = 0.24) Lumiracoxib 0.51 vs. ibuprofen 0.54 (P = 0.88)	Overall, no statistically significant difference in CV risk between groups. Higher incidence of acute MI associated with lumiracoxib vs. naproxen (see text) but not vs. ibuprofen.
Rofecoxib	VIGOR ⁴ N = 8,076 RA patients (4% of patients qualified for low-dose prophylaxis)	Rofecoxib 50mg QD vs. Naproxen 500mg BID	Recent CHD excluded. ASA not allowed.	Thrombotic events at 10 months: Rofecoxib = 0.4% Naproxen = 0.1%	5-fold difference in rate of MI between rofecoxib and naproxen treatment arms (P not reported). Among patients that qualified for low-dose ASA, the rofecoxib arm trended toward a higher rate of MI.
	APPROVe ¹⁶ N = 2,600 patients with hx of colorectal adenomas	Rofecoxib 25mg QD vs. placebo	ASA allowed.	Rate of MI/stroke at 18 months (interim analysis): Rofecoxib = 3.5% Placebo = 1.9%	Statistically significant increase in risk of MI/stroke with rofecoxib vs. placebo (P not reported). Trial halted prior to 3-year endpoint.
Valdecoxib	Unpublished ³ N = 1,636	Placebo or parecoxib (P) 40mg load then 20mg iv BID x 3 days then placebo or valdecoxib (V) 20mg BID x 7 days	Post-CABG patients.	Incidence of CV thromboembolic events; Placebo/Placebo = 0.5% Placebo/Valdecoxib (V) = 1.1% Parecoxib (P)/Valdecoxib (V) = 2.0%	Statistically significant difference (P = 0.033) in CV events in P/V group vs. placebo. Trend towards an increase in CV events in placebo/V vs. placebo/placebo group.
	Ott, et al. ¹⁹ N = 462	Parecoxib (P) 40mg iv BID x 3 days then valdecoxib (V) 40mg BID x 14 days vs. "standard of care" opioids and APAP	Post-CABG patients.	Acute MI: P/V 1.6% vs. control 0.7% (NS) Cerebrovascular event: P/V 2.9% vs. control 0.7% (NS)	A non-statistically significant higher incidence of CV and cerebrovascular events in the parecoxib/valdecoxib arm vs. the standard of care control arm.

Valdecoxib is the most COX-2 selective agent currently marketed in the United States. Its association to heightened cardiovascular risk severely limits its role in current therapy.

Some practitioners now view selective COX-2 inhibitors as therapies of last resort.

September of 2004, the validity of the VIGOR trial findings were confirmed by the early release of data from the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial.¹⁶ The interim results of this placebo-controlled trial demonstrated an undeniable increase in the rate of MI or stroke in patients treated for 18 months with therapeutic doses of rofecoxib (see Table I) and prompted the withdrawal of rofecoxib from the market.

Heightened concern that the increase in risk of cardiovascular events associated with rofecoxib is likely to be a class effect of selective COX-2 inhibitors is grounded in the theoretical evidence summarized above and extends to evidence drawn from randomized clinical trials of other COX-2 inhibitors (see Table I). For example, a definite link to an increase in the risk of serious cardiovascular outcomes has been established between valdecoxib and its prodrug (parecoxib) following coronary-artery bypass grafting²⁰ and the valdecoxib labeling has been revised to include a contraindication for its use in post-CABG patients.³ Lumiracoxib in comparison to naproxen was associated with an excess of myocardial infarctions in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) (0.38% vs. 0.21%; hazard ratio 1.77 [95% CI

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If the use of a COX-2 inhibitor is warranted, lower doses given for the shortest possible period are preferred over higher doses.

A conservative approach for practitioners is to preferentially choose from agents in the middle of the spectrum shown in Figure 2 (e.g., fenoprofen, sodium salicylate).

An alternative approach is to combine NSAID therapy with a proton pump inhibitor (such as omeprazole) or the use of misoprostol; both have been shown to prevent NSAID-induced gastroduodenal ulcers.

Acetaminophen is a reasonable choice for patients who are not able to tolerate NSAIDs and the American College of Rheumatology still advocates acetaminophen as a first-line agent for the treatment of noninflammatory osteoarthritis.²⁸

The results of ongoing clinical trials are expected to seal the fate of the COX-2 selective inhibitors remaining on the market.

0.82-3.84]).¹⁵ Although the differences detected in some trials were not statistically significant, the studies were not designed *a priori* as cardiovascular outcome studies. Therefore, the power of the trials may be inadequate to definitively detect small differences in the rates of MI. Despite this limitation, the trend toward an increase in the incidence of myocardial infarction across diverse coxib clinical trials, further suggests that cardiovascular risk appears to be a class effect of selective COX-2 inhibition.

The relative cardiovascular safety of celecoxib remains undetermined. While not statistically significant, patients in the essentially equivalent COX-2 selective celecoxib and diclofenac groups (see Figure 2) experienced more cardiovascular events than patients taking ibuprofen in the Celecoxib Long-term Arthritis Safety Study (CLASS).²¹ Recent data released from the National Cancer Institute regarding the use of celecoxib for colon cancer prevention (Adenoma Prevention with Celecoxib [APC] trial) showed a 2.5-fold increase in cardiovascular risk for patients taking 400mg/day and a 3.4-fold increase in risk for patients taking 800mg/day of celecoxib when compared to placebo² (also see Table I). However, two observational studies have not reported celecoxib to contribute to cardiovascular events.^{22,23} In addition, the National Cancer Institute also recently released interim data from the ongoing Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial, which has not yet shown that celecoxib increases cardiovascular events in patients with prior colon polyps.²⁴ As discussed earlier, celecoxib is the least COX-2 selective of the 'coxib' drug class and also has affinity for the COX-1 isoform^{8,9} (also see Figure 2). Consequently, it may potentially have properties of a COX-1 inhibitor, especially at higher doses when isoform specificity is thought to be lost.⁸ This point is further illustrated by the Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial (CRESCENT), a randomized double-blind study which looked at the effects of rofecoxib, celecoxib and naproxen on blood pressure in patients in osteoarthritis, hypertension, or type 2 diabetes mellitus.²⁵ The investigators found a small but statistically significant increase in systolic blood pressure (3.78 and 3.85mm Hg, respectively) for rofecoxib compared to celecoxib and naproxen after 6 weeks of use. These results suggest that celecoxib does not effect renal or epithelial vasculature to the same degree as rofecoxib and thus may not be associated with the same magnitude of cardiovascular risk as more selective COX-2 inhibitors.

Based on the preponderance of the evidence, the present role of COX-2 selective agents in current therapy is limited. Highly selective COX-2 NSAIDs are no longer preferred in patients with identifiable CV risk factors, and it is possible that selective COX-2 inhibitors also increase the risk of CV events in others without known risk factors. While clinical trials have confirmed a slight benefit for gastro-duodenal tolerability of the selective COX-2 inhibitors when compared to COX-1-selective NSAIDs,^{4,21} the GI benefits are lost in patients taking aspirin.²⁶ Highly selective COX-2 agents (e.g., valdecoxib) thus appear to be second- or even third-line alternatives for younger patients without identifiable CV risks when there is a positive history of gastroduodenal ulcers. For patients with identifiable cardiovascular risks and a history of NSAID-associated GI intolerance, a conservative approach for practitioners is to choose from agents in the middle of the spectrum shown in Figure 2 (e.g., fenoprofen, sodium salicylate). For patients who fail these non-selective agents, a more COX-1 selective alternative (i.e., naproxen) can be chosen to avoid increasing CV risk or a more COX-2 selective alternative (i.e., diclofenac) can be chosen to diminish GI intolerance. An alternative approach is to combine therapy with use of a PPI (such as omeprazole) or misoprostol.²⁷ While both omeprazole and misoprostol have been shown in clinical studies to be effective in preventing NSAID-induced gastroduodenal ulcers, low dose

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Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost [‡]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Palonosetron (Aloxi)	Injection: 0.25mg/5mL	5-HT ₃ receptor antagonist	Antiemetic	0.25 mg x 1 dose administered ~30 minutes before the start of chemotherapy.
	Added to formulary limited to use in oncology for the prevention of delayed, chemotherapy-induced nausea and vomiting in patients who have failed ondansetron.			
Gatifloxacin (Zymar)	Ophthalmic solution: 3 mg/mL (2.5mL, 5mL)	4th generation fluoroquinolone antibiotic	Conjunctivitis	1 drop q 2h while awake, up to 8 times/day.

* Refer to product labeling for full prescribing information. ‡ Contact pharmacy for information on drug costs.

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References available on request.

misoprostol (200mcg QID) has also been shown to be superior to omeprazole in ulcer healing.²⁷ The major limitation of misoprostol is tolerability, with abdominal pain and diarrhea being the main culprits to patient adherence. Arthrotec^R is a combination of diclofenac and misoprostol, which if tolerated, can be a rational long-term choice for NSAID users who are at high risk for ulcer formation. Another reasonable choice for patients who are intolerant of NSAIDs is acetaminophen.

In conclusion, when the use of an NSAID is necessary, it is important to assess both the patient's cardiovascular risk as well as any history of NSAID-associated gastrointestinal intolerability. COX-2 inhibitors can no longer be recommended as first-line anti-inflammatory agents because the GI benefits of selective COX-2 inhibitors do not outweigh the cardiovascular peril in patients who are at risk for thromboembolic events, and particularly in patients taking aspirin. The use of a more conservative approach to favor the selection of NSAIDs with balanced COX-isoform selectivity (as illustrated in Figure 2) is suggested.

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