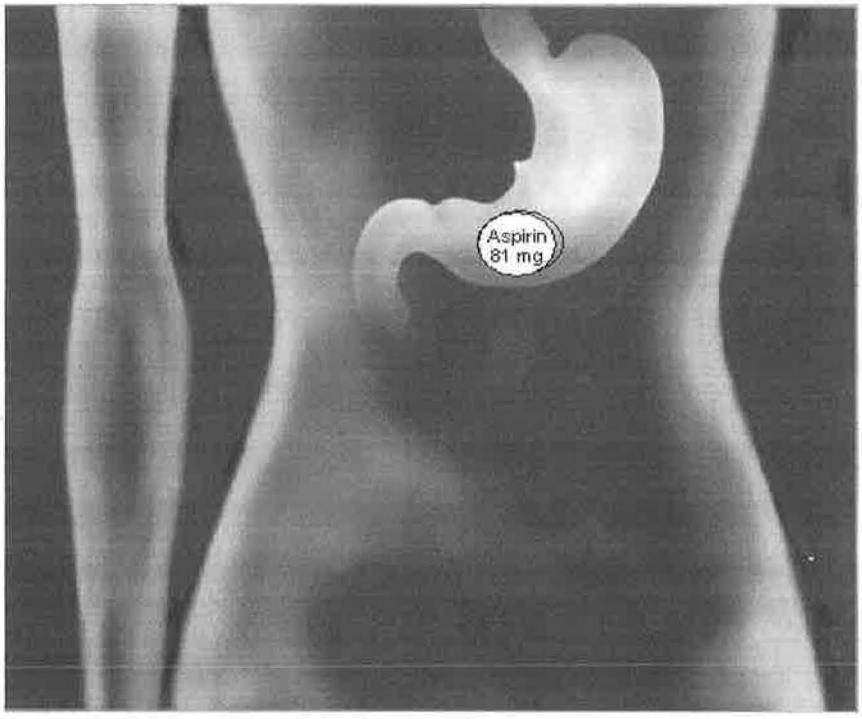
Gastrointestinal Toxicity with NSAIDS in 2004: A Revised Approach to Risk Reduction



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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used classes of drugs worldwide. Currently there are 25 different NSAIDs available by prescription in the United States (U.S.), 5 of them salicylate-based compounds and for which specifically inhibit cyclooxgenase-2 (COX-2) (Table 1) [1]. All NSAIDs are currently orally-administered with the exception of ketorolac, the only available parentally administered NSAID. In the U. S., three additional COX-2 specific inhibitors, lumiracoxib, etoricoxib and parecoxib, are under review for consideration for approval by the U.S. Food and Drug Administration (FDA). Among the COX-2 inhibitors in clinical development, parecoxib is the only NSAID which is parenterally-administered.

Table 1 . List of NSAIDs Available by Prescription

Traditional Non-Salicylates	Salicylates	COX-2 Inhibitors
Diclofenac (Voltaren)	Aspirin[a] (Zorprin, Easprin)	Celecoxib (Celebrex)
Diclofenac/Misoprostol (Arthrotec)[b]	Diflunisal (Dolobid)	Valdecoxib (Bextra)
Fenoprofen (Nalfon)	Salsalate (Disalcid, Salflex)	Etodolac (Lodine)
Flurbiprofen (Ansaid)	Choline salicylate (Trilisate)	Meloxicam (Mobic)
Ibuprofen (Motrin)[a]	Magnesium salicylate (Magan)	
Indomethacin (Indocin)		
Ketoprofen (Orudis)[a]		**In Clinical Development:**
Ketorolac (Toradol)[c]		Etoricoxib[d]
Meclofenamate		Lumiracoxib[e]
Mefenamic acid (Ponstel)		Parecoxib [f]
Nabumetone (Relafen)		
Naproxen (Naprosyn, Anaprox)[a]		
Oxaprozin (Daypro)		
Piroxicam (Feldene)		
Sulindac (Clinoril)		
Tolmetin (Tolectin)		

[a] Also available as over-the-counter preparations in the United States in 2004
[b] Combination tablet of NSAID/synthetic prostaglandin E_1
[c] Parenterally administered
[d] Tablet in clinical development by Merck & Co., Inc. (West Point, PA)
[e] Tablet in clinical development by Novartis (East Hanover, NJ)
[f] Parenterally administered; In clinical development by Pharmacia Inc (Peapack, NJ)

Although these agents are effective in relieving the signs and symptoms of inflammatory conditions, such as rheumatoid arthritis (RA) and osteoarthritis (OA), their use may be limited by the occurrence of drug-induced side effects, including dyspepsia, gastric and duodenal ulcers, and potentially life-threatening ulcer complications (e.g., hemorrhage, gastric outlet obstruction, and perforation) [2-3]. NSAID-induced ulcers and ulcer complications represent a significant health hazard in the United States. Conservative calculations estimate that approximately 107,000 patients are hospitalized each year for NSAID-related gastrointestinal (GI) complications and that at least 16,500 NSAID-associated deaths occur annually among arthritis patients alone[3] - probably the largest number of deaths attributable to any class of therapeutic agents in this country. More recently, cardiovascular complications and mortality have been recognized and attributed to some members of the NSAID class, in particular some of the COX-2 specific inhibitors. In some instances, however, NSAIDs' anti-platelet effects are beneficial, such

as with aspirin for cardiovascular prophylaxis. Although, the cardiovascular morbidity and mortality attributable to NSAIDs has not yet been quantified, the sum of total adverse events associated with this class of agents has created a great deal of interest in the adverse event profile of NSAIDs.

Since the upper gastrointestinal side-effects constitute the greatest of the untoward effects of NSAIDs, this review will concentrate on recent information pertaining to untoward gastrointestinal effects of NSAIDs.

MECHANISMS OF TOXICITY OF NSAIDs

Irrespective of site of gastrointestinal damage, the mechanisms through which NSAIDs cause injury are similar throughout the tract. The general mechanisms can be grouped into two categories: 1) those dependent on inhibition of the enzyme, cyclooxygenase and, 2) those independent of cyclooxygenase inhibition. The later category is composed of topical mucosal toxic processes.

Topical Effects

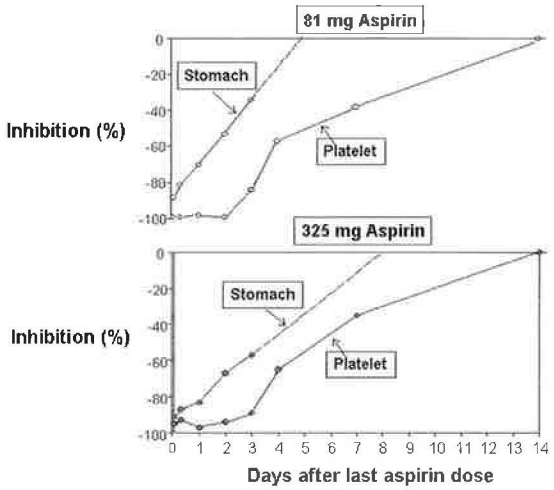
Considerable evidence exists that aspirin and other NSAIDs injure the gastrointestinal mucosa, in part, by a direct topical effect. Within a few minutes of NSAID ingestion, NSAIDs accumulate intracellularly at very high concentrations causing denudation of surface epithelial cells and increased mucosal permeability. Another topical mechanism of NSAID injury is an attenuation of the phospholipid content and surface hydrophobicity of the gastric mucus gel layer. [4] Topical effects of NSAIDs are likely the major mechanism responsible for acute hemorrhages and erosions observed acutely after NSAID challenge. Enteric coated NSAIDs will produce considerably less acute topical erosive and hemorrhagic injury than plain, non-enteric-coated formulations during short-term (one to two weeks) administration [5,6], an observation in support of a local toxic effect of NSAIDs. However, with long-term administration of enteric-coated formulations, gastric ulcers develop at rates that are not different than with non-enteric coated preparations[7], presumably as a result the systemic mechanism of injury.

Cyclooxygenase inhibition

The beneficial effect of NSAIDs to decrease systemic inflammation and their deleterious effects in the gastrointestinal tract are both, in part, related inhibition of the enzyme, cyclooxygenase. Within the gastrointestinal tract, NSAID associated reduction in gastroduodenal mucosal prostaglandin concentrations is the major contributor towards NSAID mucosal toxicity. Cyclooxygenase, the rate-limiting enzyme in prostaglandin synthesis, is inhibited by NSAIDs. Most NSAIDs (with the exception of COX-2 specific inhibitors), via inhibition of cyclooxygenase, will reduce gastroduodenal prostaglandin mucosal concentrations resulting in the loss of a major mechanism for protection against mucosal injury. Aspirin, by acetylation of cyclooxygenase, inhibits this enzyme irreversibly, while all other NSAIDs inhibit cyclooxygenase in a reversible, concentration-dependent manner. With aspirin, when cyclooxygenase is irreversibly inhibited, the capacity for prostaglandin synthesis does not return to normal for several days until new enzyme can be synthesized.[8] A recent study has demonstrated that after low daily doses of aspirin,

prostaglandins do not fully recover in the stomach for approximately 5 to 8 days and in the platelet until 14 days (**Figure 1**). This may explain, why aspirin, in comparison to the other NSAIDs is one of the most potent inhibitors of prostaglandin and thromboxane synthesis.

Figure 1.
Time course of recovery of gastric mucosal prostaglandins and platelet thromboxane after aspirin. Inhibition (compared with placebo) of prostaglandin synthesis in the stomach and of platelet thromboxane B_2 production as a function of days after the last dose of a 46-day treatment course with 81 mg of aspirin daily (above) and aspirin 325 mg every third day (below). Data shown as solid lines are actual data derived from the study. Dashed lines are extrapolations using linear regression equations. Data from reference [8].



In the early 1990s, two structurally-related COX isoforms were identified in mammalian cells, COX-1 and COX-2. COX-1 is found in most of the body's tissues, including the stomach. COX-2, by contrast, is believed to be the principal COX isoform that participates in inflammation and there is little COX-2 activity present in the stomach or platelet. In studies of the human gastrointestinal tract, little to no COX-2 protein or activity has been demonstrated, while abundant COX-1 protein and activity have been observed.[10,11] This concept has led to development and clinical introduction of COX-2 specific NSAIDs. Recent animal data indicate that for gastric ulceration to occur, both COX-1 and COX-2 must be inhibited.[12] Interestingly, in one model selective inhibition of COX-1 alone does note cause gastric damage.[12] Thus, the actual reason for COX-2 specific inhibitors being associated with improved GI toxicity may more closely relate to their lack of dual COX isoform inhibition rather than simply their COX-1 sparing effects.

ADVERSE GASTROINTESTINAL EFFECTS OF NSAIDS

Much of the difficulty in attempting to quantify adverse effects events attributable to NSAIDs arises from the number of ways in which NSAID-induced adverse effects can be defined. Symptoms, endoscopic mucosal lesions, and most importantly, serious GI events have all been ways the magnitude of NSAIDs' effects have been assessed, with the serious upper GI complications being the most relevant to NSAIDs' clinical morbidity. The Food and Drug Administration reports that symptomatic gastrointestinal ulceration (that is, ulcers associated with pain, perforation, bleeding or obstruction) occurs in approximately 2 to 4% of patients treated with an NSAID for one year.[3]

RISK GROUPS FOR NSAID-INDUCED ULCERS

Certain groups of NSAID-taking patients appear to be at greater risk for development of NSAID ulcer complications (Table 2) and should, therefore, be given greater consideration for strategies to prevent or to reduce ulceration. The most significant risk factor for a NSAID-induced complication is a history of prior peptic ulcer disease or a

prior ulcer complication, factors that increase the risk for NSAID-induced GI events by two- to fourfold [14-17].

Table 2. Risk factors for NSAID-induced ulcers

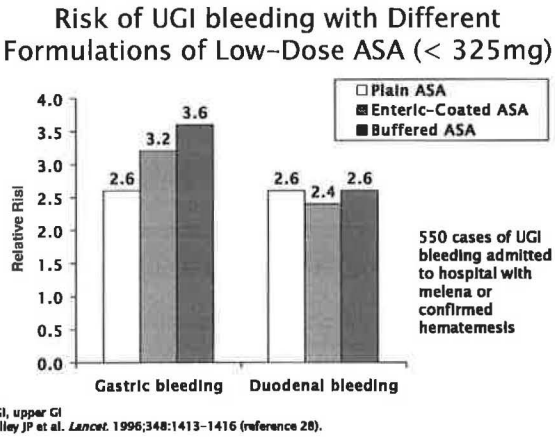
Definite	Possible
Prior peptic ulcer disease	*Helicobacter pylori*
Prior NSAID gastrointestinal complication	Smoking
Advanced age	
Concomitant use of corticosteroids	
Concomitant use of anticoagulants	
High doses of NSAIDs, multiple doses or combinations of NSAIDs	
Comorbid diseases	
Ethanol use	

Advancing age is also a risk factor. Although there does not appear to be a threshold age at which risk dramatically increases, the risk increases linearly at rate of approximately 4% per year of advancing age.[14] There have been conflicting data as to the role that duration of NSAID exposure has in the risk for NSAID-related GI events. Some case-control studies have suggested that the risk of NSAID-associated gastrointestinal complications is highest within the first thirty days of NSAID use.[18,19] More recently, however, controlled prospective studies of arthritis patients chronically taking NSAIDs indicate that the risk of serious NSAID-induced gastrointestinal complications appears to be cumulative and linear.[15-17] It has become clear from epidemiologic studies that as the dose of a NSAID increases, the risk of ulcer complications also increases in a parallel fashion.[14,18] This dose-response relationship is seen across all classes of NSAIDs and is also linear. Concurrent use of more than one NSAID is also a risk factor since this practice essentially increases total NSAID dose, the most common example being the combined use of prescribed NSAIDs and OTC NSAIDs. Other risk factors are concomitant use of corticosteroids or anticoagulants, or comorbid conditions such as significant heart disease or rheumatoid arthritis.[1,15,20] However, the use of corticosteroids alone does not independently cause ulcer disease.[21] Recent data indicate that regular alcohol consumption combined with regular NSAID use is an additive risk factor for serious upper GI adverse events.[22,23] Interestingly, regular use of low doses of aspirin increases upper GI risk in those frequently consuming alcohol. Among current drinkers, aspirin taken at least every other day at a dose of 325 mg/day or greater is associated with a sevenfold increased risk of upper GI bleeding when compared with those who do not drink or use low-dose aspirin.[23]

Low-Dose Aspirin

Low daily doses of aspirin (usually 325 mg per day or less) are very commonly prescribed for prevention of cardiovascular and cerebrovascular diseases. In controlled studies of low-dose aspirin, aspirin therapy increased risks of GI bleeding[24] and increased the likelihood of hospitalization for ulcers.[25] In a case-control study, aspirin use as low as 75 mg per day has been associated with greater than a two-fold increased risk of GI bleeding.[25] One controlled study of placebo and aspirin doses of 300 mg/day and 1200 mg/day prescribed for prevention of cerebrovascular events reported rates of gastrointestinal bleeding of 0.1%, 0.3% and 0.6%, respectively, an odds ratio of 3.6 fold increased risk for aspirin 300 mg/day over placebo.[26] More recently, a case-control study has indicated the odds ratio for upper GI bleeding for doses of aspirin of 300 mg./day or less is 2.4.[27]

Figure 2.



Buffered or enteric-coated aspirin preparations when dosed at 325 mg/day, while probably associated with a reduced incidence of dyspepsia when compared to plain aspirin, unfortunately have risks of upper GI bleeding that are similar to plain aspirin (**Figure 2**).[28]

As discussed in the section on safer NSAIDs, when dosed concurrent with a COX-2 specific inhibitor in a large GI outcomes trial, aspirin at a dose of 325 mg/day or less reduces the beneficial GI effects associated with celecoxib.[16]

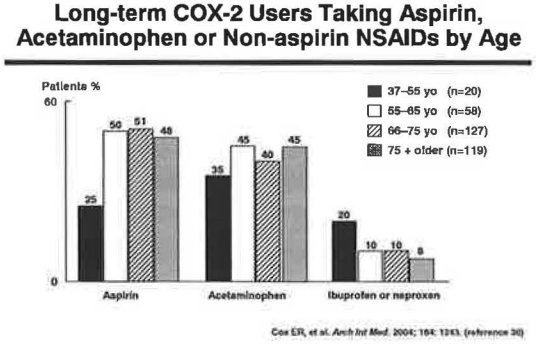
The sum of these data on risks and benefits of low daily doses of aspirin indicate that any formulation of aspirin at doses as low as 325 mg per day or less, while beneficial for vascular prophylaxis, are associated with at least a two-fold and possibly as high as four-fold increased risk of gastrointestinal complications. Such conclusions have led to investigations evaluating toxicity of aspirin doses lower than 325 mg per day. In a study of low-dose aspirin administered for 3 months, 10 mg of daily aspirin per day significantly lowered gastric mucosal prostaglandins and caused gastric ulceration.[29] Even when dosed as infrequently as 81 mg every third day, aspirin at this dose and interval continues to significantly suppress gastric prostaglandins for approximately five days after aspirin dosing.[8] Thus, it appears unlikely that there is an orally-administered dose of aspirin that is efficacious for cardiovascular prophylaxis that is also without gastrointestinal risks.

Undocumented Use and Over-the-Counter NSAIDs

Precise quantification of NSAID risk is complicated by undocumented NSAID consumption. Total NSAID usage is probably underestimated given the recent OTC availability of NSAIDs. Numerous OTC compounds are available which contain aspirin or other NSAIDs. In the United States at the time of this writing, aspirin, ibuprofen, naproxen and ketoprofen are available over the counter. Unfortunately, in many instances both the patient and physicians are unaware that such compounds are being taken.

Often OTC NSAIDs and aspirin are taken concurrently with prescribed NSAIDs or COX-2 inhibitors. A recent study of patterns of OTC aspirin and NSAID use in large pharmacy benefits plan consisting of 95,000 members revealed that among patients who receive COX-2 inhibitors, 50% take concomitant aspiring and 10% take a concomitant OTC NSAID. (**Figure 3**)

Figure 3.



Helicobacter pylori and NSAIDs

NSAIDs and the bacterium, *Helicobacter pylori (H. pylori)*, are the two main etiologies for gastroduodenal ulcers. There are many characteristics of NSAID-induced ulcers and *H. pylori*-related ulcers to suggest that these two types of ulceration are separate pathophysiologic entities. Data on whether *H. pylori* contributes to the risk of NSAID-induced gastrointestinal mucosal injury have been conflicting. For example, some studies indicate that eradication of *H. pylori* before starting NSAIDs reduces NSAID-induced ulcers.[31] However, other data indicate that *H. pylori* eradication in patients with a history of peptic ulcer disease does reduce NSAID-induced.[32] More recently, several other studies have assessed the potential interaction between *H. pylori* and NSAIDs and have provided results that have been similarly discrepant.[33, 34,35] These conflicting conclusions are probably explained by differences in patient populations, study designs, doses, duration, and types of NSAIDs evaluated throughout the various studies. The data are more consistent regarding a synergistic injurious GI effect between *H. pylori* and aspirin than between *H. pylori* and non-aspirin NSAIDs. [36, 37]

Esophageal Ulcers and Strictures with NSAIDs

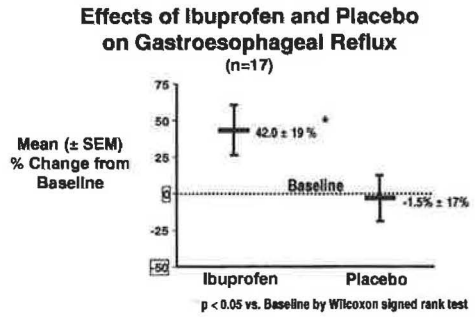
The principle toxic manifestations of NSAIDs in the esophagus are ulcers and strictures. However, esophageal ulcers are not specific to NSAIDs and has been reported in association with at least 26 different medicines.[38,39] Considering all of the medicines associated with esophageal ulceration, the incidence of NSAID-associated ulceration falls about in the middle of the group. There is not a likely single unifying mechanism to explain all pill-induced esophageal ulceration. With aspirin, esophageal ulcers are initiated by a disruption of the esophageal mucosal barrier to hydrogen diffusion, thus rendering the underlying esophageal mucosa more susceptible to the refluxed gastric acid.[39,40] In animal's esophageal ulceration can be experimentally induced after just a few oral doses of an NSAID.[41] The one unifying mechanism in all cases of esophageal pill ulceration is prolonged mucosal contact with a medicine with relatively caustic physical properties.

Esophageal stricture, as a complication of NSAIDs, has been less widely appreciated than has ulceration. All of the same medicines that are associated with pill-induced esophageal ulceration have also been associated with esophageal stricture.[39,42] Risk factors for pill-induced ulcers and strictures are recumbency, pill ingestion just prior to sleep or during the post-operative period, or ingestion of sustained-release pill formulations

Gastroesophageal Reflux Disease and NSAIDs

Most studies reporting NSAID-induced esophagitis have been case reports or small series.[43-45] We recently conducted a prospective-trial to assess whether, in patients with GERD at baseline, use of NSAIDS can increase gastroesophageal acid exposure (ref). In GERD patients, Ibuprofen 800 mg TID significantly increases gastroesophageal reflux by greater than 40% (**Figure 4**)[46].

Figure 4.



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THERAPY FOR NSAID-INDUCED ULCERS

Therapy for NSAID-induced ulcers needs to be tailored depending on whether one is attempting to heal an already established ulcer associated with NSAIDs or attempting to prevent an NSAID-induced ulcer from developing.

Prevention of NSAID-Induced Ulcers

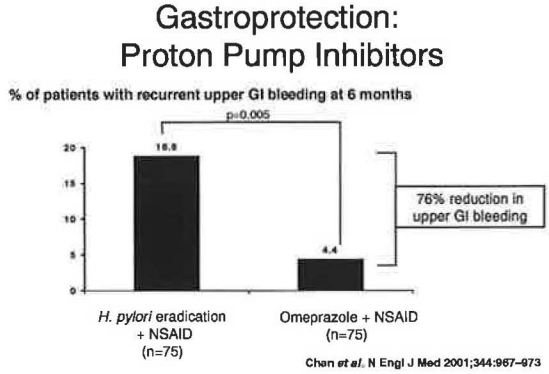
Prior to the clinical availability of safer classes of NSAIDs, reduction in NSAID-induced GI toxicity was primarily accomplished by prescribing drugs that when co-administered with NSAIDs would protect against mucosal ulceration. Ideal candidates for co-therapy are those considered as high risk for NSAID-induced ulcers (**Table 2**). Various co-therapies that have been considered are discussed in the following sections.

H_2-Receptor Antagonists. A number of studies have evaluated whether an H_2-receptor antagonist (H_2-RA), when coadministered with an NSAID, can prevent NSAID-induced ulcers. [37-39] These studies have consistently found that all four H_2-RAs, namely cimetidine, famotidine, nizatidine and ranitidine, at their usual ulcer-healing doses do not prevent NSAID-associated gastric ulcers. Because most NSAID-induced ulcers are gastric rather than duodenal, and because one cannot predict which type of NSAID-induced ulcer will develop, H_2-RAs are not ideal drugs for NSAID-ulcer prophylaxis. However, when one of the H_2-RAs, famotidine, is administered at a "high" dose (40 mg twice daily) NSAID-induced duodenal and gastric ulcers are both effectively reduced.[40]

Prostaglandins. Misoprostol, the synthetic PGE_1 analogue, reduces NSAID-induced gastric and duodenal endoscopic ulceration as well as NSAID-induced serious GI adverse events.[15] The disadvantages to misoprostol are that it may cause dose-related diarrhea and is not effective in treating dyspepsia associated with NSAIDs. The development of a combination tablet of misoprostol and the NSAID diclofenac is associated with a reduction in side effects such as diarrhea and has a favorably low ulceration rate.[41] In a recent direct comparison of misoprostol and ranitidine within the same study, the two drugs were equal in efficacy for prevention of NSAID-induced duodenal ulcers whereas misoprostol was significantly more effective than ranitidine in prevention of endoscopically diagnosed gastric ulcers.[42]

Proton Pump Inhibitors. Use of proton pump inhibitors [PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole)] as prophylaxis for NSAID ulcers has become an attractive strategy for many clinicians. Support for this practice comes from studies of endoscopic ulceration demonstrating PPIs to be more effective than ranitidine (150 mg BID)[53] or than misoprostol [54,55] for the prevention of NSAID-induced gastric and duodenal ulcers. There has also been an outcomes study demonstrating PPIs to effectively reduce NSAID-induce upper GI bleeding. As seen in **Figure 5**, in a prospective study of 150 patients with *H. pylori*-gastritis, prior to initiation of naproxen half of the cohort was given antibiotics for the eradication of their *H. pylori*.[37] The other group continued with their persistent *H. pylori* infections, but received omeprazole along with naproxen. Use of a PPI in *H. pylori*-infected patients taking naproxen was associated with a 76% reduction in incidence of recurrent upper GI bleeding over the following six months.[37]

Figure 5. Upper GI Bleeding with Proton-Pump Inhibitors and NSAIDs



Treatment of NSAID-induced Ulcers

Treatment of NSAID-induced ulcers is more straightforward than prophylaxis. When attempting to treat an ulcer that has formed during NSAID use, the first step is always to stop the NSAID. Once the NSAID is stopped, rapid ulcer healing can be achieved by treatment with standard doses of H_2-RAs.[56] For patients in whom NSAIDs cannot be discontinued, use of a PPI will allow ulcer healing, even while NSAID use continues.[56]

NSAIDs WITH IMPROVED GI SAFETY PROFILES

COX-2 Specific Inhibitors

In an effort to achieve an improved GI adverse event profile, a novel subclass of NSAIDs was developed, the COX-2-specific inhibitors. In December 1998, the first COX-2-specific inhibitor, celecoxib, was approved in the U.S., followed 6 months later by rofecoxib. They have been demonstrated in clinical trials to be as effective as traditional NSAIDs, such as ibuprofen and naproxen, yet with an improved GI safety profile. These two first-generation COX-2 inhibitors had rapid acceptance as anti-inflammatory and analgesic agents and since their introduction, other second-generation COX-2 inhibitors have been introduced into clinical practice or placed into the developmental pipeline.

Pharmacology of COX Inhibitors. Both the beneficial and deleterious effects of NSAIDs are related to inhibition of the enzyme COX. Reduction in GI mucosal prostaglandin concentration is the major contributor toward NSAID mucosal toxicity. COX acts on arachidonic acid to generate prostaglandins and thromboxane (**Figure 6**).

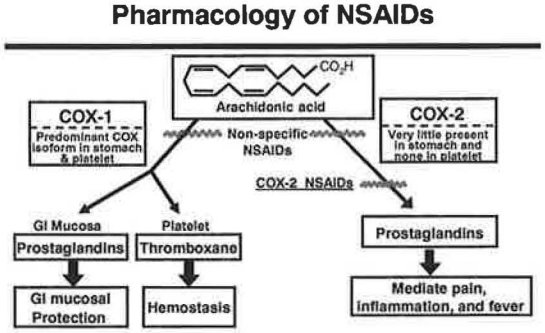


Figure 6

In the early 1990s two structurally related isoforms were identified in mammalian cells, COX-1 and COX-2. Of the many differences between the COX isoforms, one notable distinction is that COX-2 contributes very little to COX activity in the stomach or platelet. This concept has formed the basis for the development and clinical introduction of COX-2-specific NSAIDs. Before the launch of celecoxib in 1999, all previously available nonspecific NSAIDs inhibited both COX-1 and COX-2. Recent animal data indicate that for gastric ulceration to occur, both COX-1 and COX-2 must be inhibited. Interestingly, in one model specific inhibition of COX-1 alone does not cause gastric damage. Thus, the actual explanation for COX-2-specific inhibitors' improved GI toxicity relates to their lack of dual COX isoform inhibition.

Products Available and in Development. The approval of celecoxib and rofecoxib was rapidly followed by development of a second generation of COX-2 inhibitors, with other second-generation inhibitors still being developed by other companies (**Table 3**).

Table 3

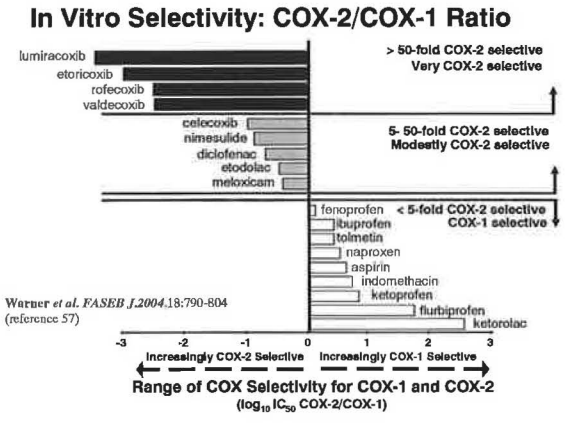
COX-2 INHIBITORS CURRENTLY OR PREVIOUSLY AVAILABLE AND IN DEVELOPMENT

	COX-2 INHIBITOR	TRADE NAME	STAGE OF DEVELOPMENT	ROUTE OF ADMINISTRATION	COMPANY
1st Generation	Celecoxib	Celebrex	Approved 1998	PO	Pfizer
	Rofecoxib	Vioxx	Approved 1999	PO	Merck
2nd Generation	Valdecoxib	Bextra	Approved 2001	PO	Pfizer
	Parecoxib	Dynastat	Phase III	IV/IM	Pfizer
	Etoricoxib	Arcoxia	Phase III	PO	Merck
	Lumiracoxib	Prexige	Phase III	PO	Novartis

Valdecoxib was the first of the second-generation COX-2 NSAIDs to receive approval for clinical use in the U.S. A fourth, etoricoxib, has been approved by the European regulatory authority, and it and a fifth, lumiracoxib, are currently under consideration for FDA approval.

The primary goal for the first generation of COX-2 inhibitors was to design pharmacologic agents with improved COX-2 selectivity over older NSAIDs. Implicit in this concept was the assumption that greater COX-2 selectivity would translate into greater clinical benefit. Consequently, all of the second-generation coxibs are more COX-2 selective than the predecessor developed within the same pharmaceutical company (**Figure 7**).[57]

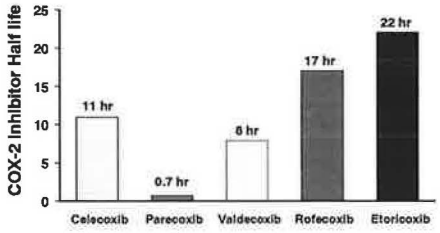
Figure 7



For example, etoricoxib has a much improved COX-2 selectivity profile over rofecoxib (both Merck products, Whitehouse Station, NJ). Also, parecoxib and valdecoxib, Pharmacia's (Peapack, NJ) next-generation coxibs, have an in vitro selectivity approximately 4 times that of celecoxib. Although a greater COX-2 selectivity might theoretically confer an enhanced clinical benefit to the more selective agents, the majority of clinical trial data do not suggest an improvement in efficacy or safety profiles of the second-generation coxibs compared with the first-generation agents.[58] In fact, it appears that and increased degree of COX-2 selectivity may be closely associated with an increased risk of adverse effects.

Pharmacokinetic serum half-lives are variable among the COX-2 inhibitors (**Figure 8**).[59]

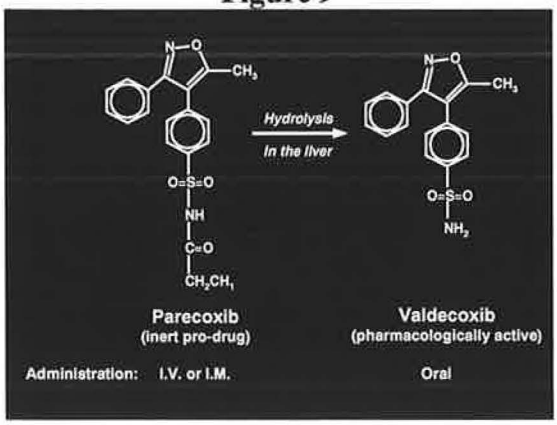
Figure 8



The duration of NSAIDs pharmacodynamic effects usually parallels the amount of time of its circulating presence. Among the currently FDA-approved COX-2 inhibitors, celecoxib and valdecoxib (half-lives of 11 and 8 hours, respectively) are approved for twice-daily administration, compared with rofecoxib, (half-life of 17 hours), which is approved for once-daily dosing. On the other hand, the potential downside to a longer half-life is the longer duration of exposure to the adverse pharmacodynamic effects of a COX-2 inhibitor.

Valdecoxib/Parecoxib. Two related compounds, valdecoxib and parecoxib, are second-generation products (**Figure 9**). Parecoxib is a parenteral compound that, if approved in the U.S., will be the only COX-2 inhibitor for intravenous (IV) or intramuscular (IM) use.

Figure 9



Another unique aspect of parecoxib is that it is a pro-drug that is pharmacologically inactive when administered and produces no analgesic or anti-inflammatory effects in itself. However, after injection parecoxib is enzymatically hydrolyzed in the liver to its active moiety valdecoxib. Therefore, parecoxib's relatively short serum half-life (~45 minutes) is not reflective of the duration of its clinical effects. When the FDA evaluated its new drug application in July 2001, parecoxib was not approved in the United States on the basis of the need for further studies. In Europe, however, parecoxib was approved for clinical use in November 2001. Valdecoxib, parecoxib's orally administered metabolic derivative, was approved for clinical use in the United States by the FDA in 2001 for the treatment of osteoarthritis, rheumatoid arthritis, and the treatment of dysmenorrhea.

Endoscopic and Clinical GI Outcome Studies. Short-term [60] and long-term [61-64] endoscopic studies of patients taking COX-2 inhibitors have demonstrated incidences of gastroduodenal endoscopic ulceration of approximately 3 to 5% (rates similar to placebo) when compared to traditional NSAIDs which have a 20 to 40% incidence of endoscopic gastroduodenal ulcers. However, as has been observed in a number of other NSAID studies, endoscopic ulceration is generally asymptomatic and is usually without untoward clinical consequences. Thus, the more clinically meaningful data are those which report incidences of serious GI adverse events such as ulceration associated with perforation, pain or bleeding. In two separate retrospective analyses of combined clinical trials assessing the therapeutic efficacy of COX-2 inhibitors in arthritis patients, treatment with rofecoxib or celecoxib was associated with significantly lower incidences of serious upper GI adverse clinical events than with comparator NSAIDs.[63,66]

Prospective clinical trials designed to assess whether COX-2 inhibitors are associated with reductions in upper GI complications have been conducted. The acronyms for the celecoxib, rofecoxib and lumiracoxib outcome studies are CLASS (Celecoxib Long-term Arthritis Safety Study)[16], VIGOR (Vioxx Gastrointestinal Outcomes Research)[17] and TARGET [67]trials. The CLASS and VIGOR trials evaluated approximately 8000 arthritis patients and reported an approximately 50% reduction in upper GI events with celecoxib and rofecoxib, statistically significant differences when compared to non-selective NSAIDs. The TARGET trial which evaluated more than 18,000 osteoarthritis patients a 66% reduction in ulcer complications was observed with lumiracoxib when compared to traditional NSAIDs. [67]

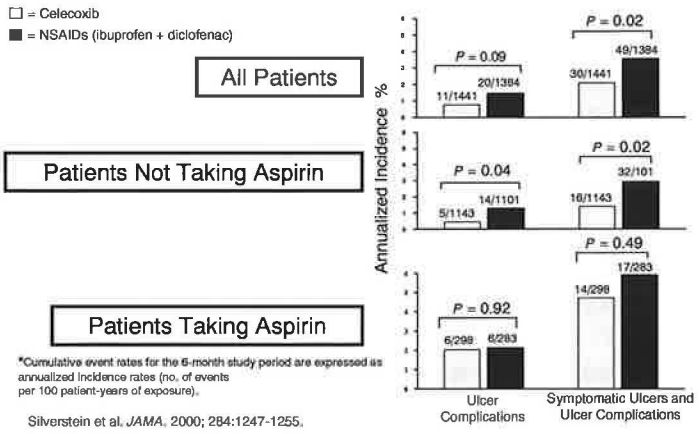
The above endoscopic and outcome trials support the contention that COX-2 specific inhibitors have improved gastrointestinal safety when compared to traditional NSAIDs. However in gastrointestinal processes such as with an acute ulcer that is attempting to heal, the effects of COX-2 specific inhibitors may be no better than those of traditional NSAIDs. For example, traditional NSAIDs delay ulcer healing. Administration of specific COX-2 inhibitors to animals with experimentally-induced gastric ulcers also delays ulcer healing.[68,69] As gastric ulcers undergo healing and repair, COX-2 mRNA ulcer concentrations are elevated.[70]

Low-Dose Aspirin and COX-2 Specific Inhibitors. As mentioned earlier, low-daily doses of aspirin, taken alone, cause upper gastrointestinal ulceration. Several studies have now

documented that taking low-dose aspirin along with a COX-2 inhibitor mitigates the GI safety advantages of the COX-2 inhibitor.[16,67,71] In the CLASS and TARGET trials, those taking a COX-2 inhibitor with low-dose aspirin had rates of upper GI events similar to those taking non-selective NSAIDs with low-dose aspirin (**Figure 10**)[16]. Since concurrent use of low-dose aspirin is very commonly encountered in patients chronically taking NSAIDs, a COX-2 inhibitor might not be the preferred clinical approach to reduction of NSAID-induced GI injury in those taking low-dose aspirin.

Figure 10
(from reference 16)

CLASS Trial: Upper GI Complications Alone & With Symptomatic Ulcers (6 month data)

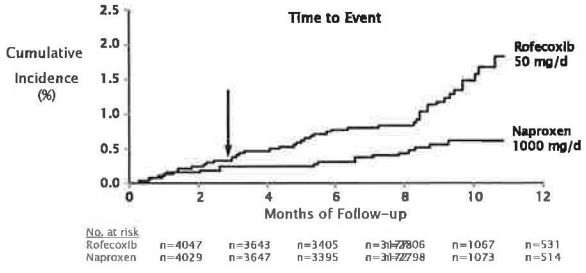


Silverstein et al. *JAMA*. 2000; 284:1247-1255.

Cardiovascular Thrombotic Events and COX-2 Specific Inhibitors. During the VIGOR trial with Vioxx™, an unexpectedly higher rate of myocardial infarction (MI) was observed with rofecoxib compared to naproxen (0.4 vs. 0.1; 95% CI for the difference 0.1-0.6%)(**Figure 11**).[17] Although this increase was a source of concern, it was argued by the sponsor that the small number of events reflected the play of chance or that the non-selective NSAID comparator, naproxen, was actually cardioprotective.

Figure 11
(from reference 17)

Cumulative Rates of Myocardial Infarction with Rofecoxib (Vioxx™) and Naproxen



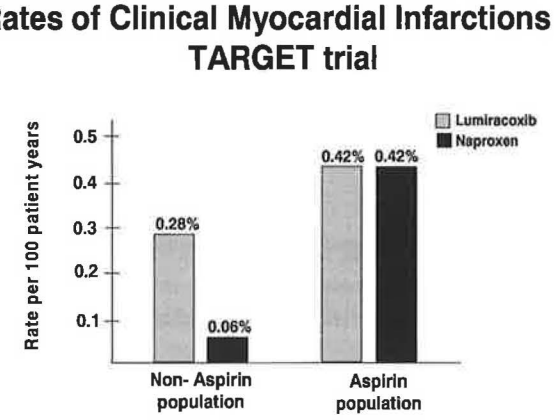
Relative risk=2.37, rofecoxib vs naproxen.
FDA Arthritis Advisory Committee Meeting, February 8, 2001; Gaithersburg, Md.

FDA, Food and Drug Administration. (Bombardier et al.; reference 17)

Study investigators attribute the lower risk of MI seen in the naproxen group to naproxen's ability to inhibit the production of thromboxane by 95% [COX-1 effect] and to inhibit platelet aggregation by 88%, and maintain this effect throughout its dosing interval. However, epidemiologic studies of possible cardioprotection afforded by naproxen have proved inconclusive.[68, 69] Rofecoxib has now been withdrawn from the market by Merck, following the premature cessation, by the data and safety monitoring board, of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study, which was designed to determine the drug's effect on benign sporadic colonic adenomas. This action was taken because of a significant increase by a factor of 3.9 in the incidence of serious thromboembolic adverse events in the group receiving 25 mg of rofecoxib per day as compared with the placebo group. Blood pressure was elevated in patients in the rofecoxib per day as compared with the placebo group. Blood pressure was elevated in patients in the rofecoxib group early in the course of the study, but the incidence of myocardial infarction and thrombotic stroke in the two groups began to diverge progressively after a year or more of treatment.

The final gastrointestinal-outcome study – the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) – was reported recently.[67, 74] TARGET compared lumiracoxib with naproxen or ibuprofen. The primary end point was the incidence of serious gastrointestinal events, which was reduced significantly among patients receiving lumiracoxib. However this difference was only observed in patients who were not taking aspirin. Although the trial, much like the CLASS trial, was not powered to detect a difference in the rates of cardiovascular events in non-aspirin users, more such events occurred in the lumiracoxib group than in the other group (0.26 vs 0.18 per 100 patient-years; hazard ratio, 1.47), although the difference was not significant. Thromboembolic events in the TARGET trial were defined as events which were "definite or probable", rendering the non-significant hazard ration of ~ 1.5 for cardiovascular events with lumiracoxib. However, when considering only the fully adjudicated myocardial infarctions which were clinically apparent, there was almost a 5-fold increase in MI in the lumiracoxib group when compared to naproxen (**Figure 12**).[74]

Figure 12 (from reference 74)



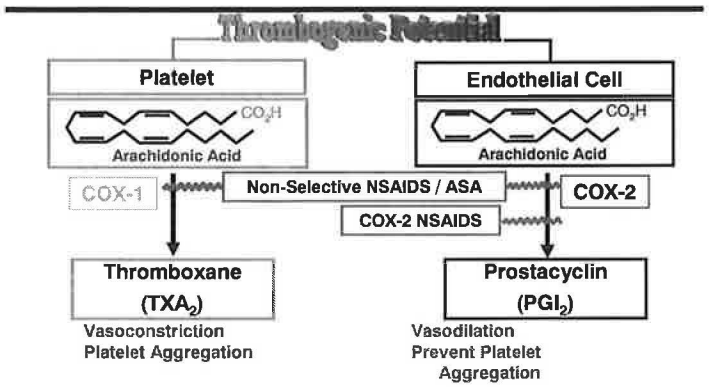
Farkouh ME *et al. Lancet 2004; 364:675-685*

In a study in patients undergoing coronary-artery bypass grafting,[75] treatment with the valdecoxib pro-drug, parecoxib, was associated with a cluster of cardiovascular events, and the drug's application for approval was rejected by the FDA. In response to the observed cardiovascular concerns, a follow-up, much larger study was conducted (CABG II), a study of the effects of parecoxib/ valdecoxib in a similar patient population. In October 2004, preliminary results of CABG II became available and once again a higher rate of myocardial infarction was observed in the parecoxib/valdecoxib-treated patients. Although parecoxib is effective as an analgesic only when converted to valdecoxib *in vivo* (**Figure 9**) and approval of valdecoxib was based on studies in patients with low cardiovascular risk, the labeling of valdecoxib does not reflect the investigational experience with parecoxib.

There is now clear evidence of an increase in cardiovascular risk with COX-2 inhibitors, an observation which is consistent with a mechanistic explanation that may extend to all the COX-2 specific inhibitors. Prostacyclin (prostaglandin I_2) is the predominant cyclooxygenase product in endothelium, inhibiting platelet aggregation, causing vasodilatation, and preventing the proliferation of vascular smooth-muscle cells in vitro.[76] Prostacyclin is derived mainly from COX-2. The cardiovascular effects of prostacyclin contrast with those of thromboxane A_2, the major COX-1 product of platelets, which causes platelet aggregation, vasoconstriction, and vascular proliferation (**Figure 13**).

Figure 13

Mechanism of Anti-Thrombotic Effect of NSAIDs



Aspirin and traditional NSAIDs inhibit both thromboxane A_2 and prostacyclin. COX-2 specific inhibitors do not affect synthesis of thromboxane A_2 due to the absence of COX-2 in platelets. Increasing vascular laminar shear stress increases the COX-2 expression. Therefore selective COX-2 inhibition by coxibs might predispose patients to myocardial infarction or thrombotic stroke. Thus a single mechanism, prostacyclin inhibition, might accelerate atherogenesis and predispose patients receiving COX-2 specific inhibitors to an exaggerated thrombotic response after rupture of an atherosclerotic plaque. The higher a patient's intrinsic risk of cardiovascular disease, the more likely the potential that this underlying mechanism might manifest in the form of a clinical event.

It is not certain whether the cardiovascular adverse effects observed with rofecoxib, parecoxib/valdecoxib and lumiracoxib are effects which are molecule specific or whether

these effects can be generalized to the class of COX-2 selective agents. To date, no excess adverse cardiovascular thrombotic effects have been observed with agents that fall within the range of modest selectivity for inhibition of COX-2 selectivity such as celecoxib, etodolac or meloxicam. The leading mechanistic hypothesis for cardiovascular effects of COX-2 inhibition suggests that adverse thrombotic effects may be related to the degree of COX-2 selectivity. This hypothesis is bolstered by the observation that the COX-2 selective NSAIDs that have so far been associated with myocardial infarctions, rofecoxib, parecoxib/valdecoxib and lumiracoxib, are the same agents which have the greatest selectivity for COX-2 inhibition (**Figure 7**).[57] It is very likely that COX-2 inhibitors with a *modest* degree of COX-2 inhibition, such as celecoxib, etodolac and meloxicam, fall within a range of COX-2 inhibition that is sufficiently selective to confer a GI safety advantage, but not too COX-2 selective to be associated with an increase in adverse CV events. However, definitive studies assessing CV safety of these later agents have not yet been conducted.

Conclusions Regarding COX-2 Specific Inhibitors. Some important conclusions are derived from the CLASS, VIGOR and TARGET trials. First, it appears that the use of low dose aspirin may reduce or eliminate any gastrointestinal protective benefit of the COX-2 inhibitors. Furthermore, although rofecoxib, lumiracoxib (and possibly celecoxib) are associated with the benefit of reduced GI toxicity, when considering global (total body) safety, increased adverse events in other systems (i.e., cardiovascular events) may reduce or eliminate overall benefits of these agents compared to traditional NSAIDs, particularly in older patients who may be at risk for cardiovascular disease. Therefore, in patients in whom there is concern of CV risk, alternative strategies for reduction of NSAIDs' GI risks should be considered.

Older Safer NSAIDs. In addition to the COX-2 NSAIDs, several other established NSAIDs or products in development have safety profiles that indicate a documented or a potential safety advantage when compared to the NSAID class. Among the older NSAIDs, those that are clinically associated with safer GI profiles are etodolac, nabumetone, diclofencac and non-acetylated salicylates such as salsalate.[77-82] Salsalate[77] and etodolac[80,82,83] have no measurable effects on gastric COX activity, and, *in vitro* assays demonstrate that etodolac and diclofenac have a moderate degree of COX-2 selectivity (**Table4**).[57,77,83]

Table 4 (from reference 57).

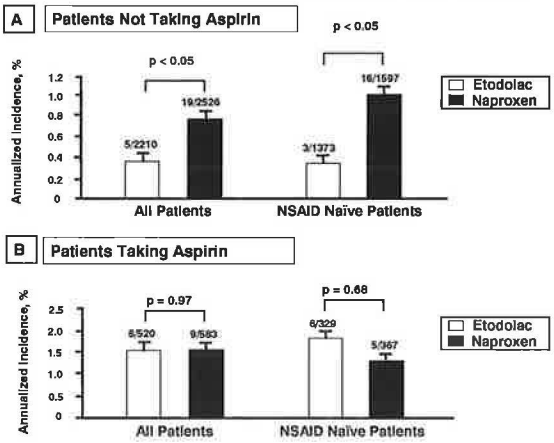
	Members	
Structural class	**Cox-1-nonselective**	**Cox-2 selective**
Alkanones	Nabumetone	
anthranilic acids	meclofenamic acid, mefenamic acid	meclofenamate esters and amides
arylpropionic acids	ibuprofen, flurbiprofen, ketoprofen, naproxen,	
diarylheterocycles		celecoxib, etoricoxib, parecoxib, rofecoxib, valdecoxib
di-tert-butyl phenols		Darbufelone
enolic acids	piroxicam, tenoxicam, phenylbutazone	Meloxicam
heteroaryl acetic acids	diclofenac, ketorolac, tolmetin	Lumiracoxib
indole and indene acetic acids	indomethacin, sulindac	etodolac, indomethacin
salicylic acid derivatives	Aspirin	
sulfanilides		nimesulide, flosulide

Meloxicam is an NSAID which has modest *in vitro* COX-2 selectivity[57,77,83] and in clinical trials has a relatively low incidence of GI ulceration.[84] However, GI ulceration and its associated risks for GI events are dose related with a higher rate of GI toxicity seen at its higher therapeutically-relevant dose. Recent clinical trials have revealed that diclofenac, one of the older non-selective NSAIDs is associated with a moderately low risk of GI ulceration [16,85,86] Although these data suggest a favorable safety profile for diclofenac, its gastrointestinal risk would be best classified as low to moderate and probably not as low as the risk associated with nabumetone, etodoloac and salsalate. The combination product of diclofenac/misoprostol (Arthrotec™) is another therapy that within one tablet combines the prophylactic component of misoprostol with an NSAID.[86,87]

Etodolac is a generic NSAID that was first approved for used by the FDA in 1991. Previous in-vitro studies have shown that etodolac is a selective inhibitor of COX-2 within the range of celecoxib.[57,83] In a 4-week, placebo-controlled study of etodolac compared with naproxen, etodolac did not inhibit gastric COX-1 or its protective prostaglandin derivatives and had endoscopically-assessed gastric safety profile that was similar to placebo.[80] I and my colleagues recently conducted a cohort study of clinically significant gastrointestinal outcomes of 16,286 patients who had taken etodolac or naproxen over a three year period.[81] Etodolac was associated with a significant 60% reduction in upper GI events, quantitatively similar to risks reductions seen in the outcome trials with celecoxib, rofecoxib and lumiracoxib (**Figures 14 & 15**).[81]

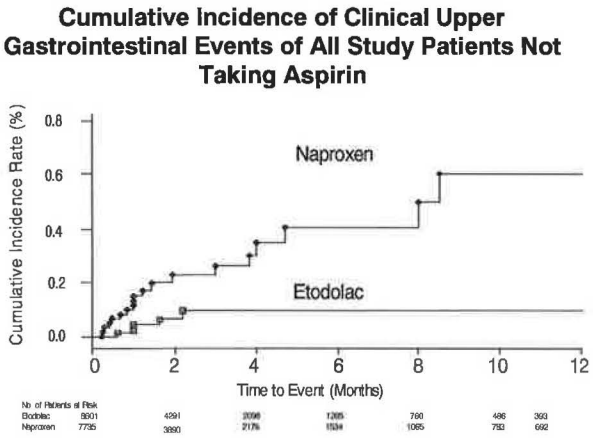
Figure 14 (from reference 81).

Rates of Clinically Significant Upper GI Events



In patients taking low-dose daily aspirin concurrent with etodolac, however, there was no difference in rates of upper GI events (**Figures 14 & 15**).[81] Therefore, etodolac in a generically-available NSAID with an upper GI safety profile similar to the celecoxib. In patients taking low-dose aspirin, a COX-2 selective agent offers no apparent GI advantage.

Figure 15 (from reference 81).



Nitric Oxide-Releasing NSAIDs. After conventional NSAIDs are administered, mucosal prostaglandins are reduced and, consequently, gastrointestinal blood flow is lowered, a process that appears to occur because of an NSAID-induced adherence of neutrophils to vascular endothelium. Nitric oxide is now recognized as a critical mediator of gastrointestinal mucosal defense, exerting many of the same actions as prostaglandins within the gastrointestinal tract. In addition to other properties, nitric oxide increases mucosal blood flow and prevents neutrophil adherence to vascular endothelium.[88] These observations have led to the development of nitric oxide (NO)-releasing NSAIDs in which the native NSAID has been coupled to a nitric-oxide releasing moiety. The concept is that a vasodilating component is delivered, by virtue of its attachment to the NSAID, directly to the gastrointestinal mucosal location that would be potentially damaged by the NSAID component. NO-NSAIDs have been synthesized using diclofenac, indomethacin, naproxen, flurbiprofen and aspirin and have been demonstrated to have the anti-inflammatory, antipyretic analgesic, and antithrombotic effects comparable with those of native NSAIDs.[88,89] However, NO-NSAIDs are not associated with NSAID-induced gastric[88,89] nor intestinal[90] toxicity that have been associated with the parent compounds. Interestingly, NO-NSAIDs inhibit both COX-1 and COX-2 and reduce gastrointestinal prostaglandins to the same extent as native NSAIDs. However, despite the marked prostaglandin reductions with NO-NSAIDs, they are not associated with the GI toxicity seen with parent compounds.

Phospholipid NSAIDs. The gastric mucosa has a hydrophobic, lipid surface, mostly caused by secretion of a surfactant-like phospholipid into the gastric mucus gel layer. Gastric surface layer phospholipid content is enriched by gastroprotective agents, such as prostaglandins, and is rapidly attenuated by NSAIDs. NSAIDs reduce surface hydrophobicity by chemically associating with and destabilizing phospholipids within the mucus gel layer, in particular phosphatidylcholine.[4] Recently, newer NSAIDs have been developed in which the native NSAID moiety has been coupled with synthetic phosphatidylcholine (PC). Animal studies using PC-NSAIDs indicate that these agents, when compared with the parent NSAID compounds, are associated with a reduction in GI ulceration and with faster ulcer healing in the face of continued NSAID exposure and have equivalent or better therapeutic activity than the native NSAIDs.[4,91,92] Recent human studies indicate that short-term courses of PC-aspirin are associated with reduction in acute gastric

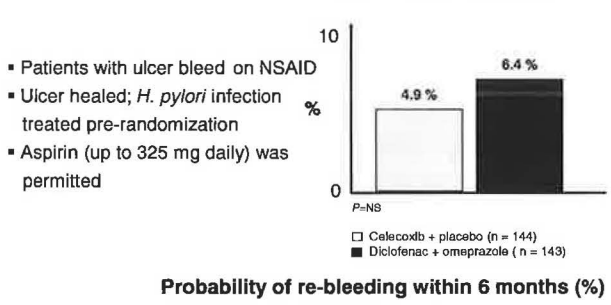
erosive injury when compared with plain aspirin.[93] Should subsequent clinical studies show continued safety and efficacy of this class of NSAIDs, PC-NSAIDs may be another future class of safer NSAIDs available to clinicians.

Traditional NSAID + Proton Pump Inhibitor

Several strategies may be employed to decrease the risk of NSAID-associated GI events. Among these strategies, there are currently two prevailing, commonly used approaches. One strategy is the use of COX-2 specific inhibitors, agents which have been demonstrated to decrease the risk of serious GI complications.[16,17] The other strategy, co-therapy with a proton pump inhibitor (PPI) also significantly reduces untoward GI outcomes associated with NSAIDs.[37] Although co-therapy with misoprostol is another approach which is effective in reducing NSAID-associated complications[15], misoprostol is very uncommonly used in clinical practice.

Numerous previous endoscopic studies have demonstrated a reduction in NSAID-associated gastroduodenal ulcers with prophylaxis with a PPI plus traditional NSAID or with a COX-2 inhibitor alone.[61,63,64,94-96] A few studies have directly compared each of these approaches, that is, PPI plus traditional NSAID versus COX-2 specific inhibitor alone.[97-99] In a previous outcomes study of patients with prior bleeding ulcers which directly compared PPI plus traditional NSAID (omeprazole plus diclofenac) to COX-2 specific inhibitor (celecoxib) alone, there were comparable rates of recurrent bleeding ulcers at 6 months of 6.4% and 4.9%, respetively.[97] A recent endoscopic trial also demonstrated comparability of these two strategies.[98] Another GI outcomes study in patients with a prior history of GI bleeding evaluated another approach, naproxen plus lansoprazole compared to celecoxib alone, and demonstrated comparable rates of recurrent ulcer complications after six months.[99] Therefore, PPI plus traditional NSAID appears to be a comparable approach to using a COX-2 specific inhibitor alone for reduction of risks of NSAID-induced GI events.

Figure 16
(from reference 97)



Chan et al. *N Engl J Med*. 2002, 347, 2104.

It is important to note that the 5% to 6% GI bleeding rates in high-risk patients at 6 months in the trial shown in **Figure 16** extrapolates to astonishingly high annual bleeding rates of 10% to 12%, rates that are higher than the 2% to 4% complication rates seen in

the general population taking NSAIDs. Each of the above-mentioned studies evaluated patients who were at high-risk for NSAID-induced ulcers, those with a previous history of upper GI bleeding. The very high ulcer rates associated with reasonable risk-reduction strategies suggests that our current management approaches of PPI plus traditional NSAID or COX-2 specific inhibitor alone may be inadequate for patients at highest risk for NSAID-induced ulceration, those with a previous history of GI bleeding. Therefore, the next logical step which might reduce ulceration and complication rates to an acceptable range in such high-risk patients would be to co-prescribe COX-2 inhibitors and PPIs as prophylactic therapy.

Some high-risk patients whose only NSAID is low-dose daily aspirin may require a PPI to reduce their risks of recurrent bleeding ulcers. A recent study demonstrated that approximately 15% of patients with a previous history of bleeding ulcers will have recurrent upper GI bleeding when taking an aspirin dose as low as 100 mg per day.[100] In similar patients taking a PPI along with aspirin 100 mg per day, rates of recurrent GI bleeding can be reduced approximately 10-fold to a rate of 1.5% of patients per year.[100]

Management Recommendations

The abundance of new information regarding strategies to reduce gastrointestinal complications associated with NSAIDs has led to a revision of recommendations for approaches to risk reduction. The change in management recommendations is mostly being directed by new information regarding cardiovascular thrombotic effects associated with the COX-2 specific inhibitors. It should be kept in mind that the guiding rationale for development of COX-2 inhibitors was to decrease the morbidity associated with the gastrointestinal complications of NSAIDs. The original problem of NSAIDs' gastrointestinal complications is 2 gastrointestinal complications per 100 NSAID-taking patients per year[1]. Given the finding in the colon-polyp trial of use of rofecoxib in low-risk patients without known cardiovascular disease of an excess of 1.6 myocardial infarctions and strokes per 100 patients[101] and, in a study of parecoxib/valdecoxib in high cardiovascular risk patients recently undergoing coronary artery bypass, an excess of 5.7 myocardial infarctions and strokes per 100 patients[75], with COX-2 specific NSAIDs we may be exchanging prevention of GI adverse effects for development of cardiovascular complications. The tradeoff here involves drugs for symptoms of arthritis and reduction of GI events, for which many alternative medications are available, in the context of serious, life-threatening cardiovascular complications. Thus, for patients in whom there is concern of cardiovascular risk, alternative strategies for reduction of NSAIDs' GI risks should be considered.

In light of the above considerations, management recommendations for reducing GI risks with NSAIDs have been revised (**Figure 17**).[102] Decisions for appropriate therapy for patients requiring NSAIDs should be primarily based on two considerations: 1)assessment of the patient's baseline GI risk (no/low NSAID-GI risk versus NSAID-GI risk) and, 2) assessment of the patient's baseline cardiovascular risks (no CV risk versus CV risk). Based on the various combinations of gastrointestinal and cardiovascular risks, evidence-based recommendations for four different patient scenarios are (**Figure 17**)[102]**:**

1) Patient with no CV and no NSAID-GI risk: Patient's low cardiovascular risk assumes that low-dose aspirin is not taken. For patients at low NSAID-GI risk who are not taking aspirin, the likelihood of a GI event is very low. Therefore these patients can be given a traditional NSAID without gastroprotective therapy. A very low number of these patients will develop GI complications. However, the low risk of GI events weighed against the high financial costs of GI risk-reduction favors traditional NSAIDs alone for the majority of these patients.

2) Patient with no CV risk but with NSAID-GI risk: In patients with *modest* GI risk for NSAID-related complications, data indicate that use of a COX-2 specific inhibitor alone or use of a traditional NSAID + a proton pump inhibitor are approaches that achieve comparable levels of GI risk reduction.[97-99] Thus either approach seems reasonable for patients with this combination of risk. There is, however, one important exception to this recommendation. Patients at highest risk for GI events, those with a previous history of GI bleeding, may not be sufficiently risk reduced with either strategy. Therefore, patients with a previous history of GI bleeding should be given a COX-2 selective agent plus a PPI*.[103] Since NSAID-GI risk reduction can be achieved at a much lower cost with etodolac when compared to labeled COX-2 inhibitors, etodolac should be the preferred COX-2 selective agent.

3) Patient with CV risk and no/low NSAID-GI risk: Until long-term studies are available evaluating cardiovascular effects of the remaining COX-2 inhibitors, the most prudent approach for patients with cardiovascular risks is to use a traditional NSAID (± a PPI*). The degree of GI risk or the need for low-dose aspirin will direct whether the PPI* should be added or not.

4) Patient with CV risks and NSAID-GI risk: These patients' baseline risk for NSAID-GI complications is high and a major GI bleed could lead to significant cardiovascular complications. Thus, non-NSAID therapy should be considered. If a traditional NSAID is prescribed, a PPI* should be added.

* Misoprostol can be substituted for a PPI.

Figure 17

A Clinicians' Guide to NSAID Therapy

	No/Low NSAID GI Risk	NSAID GI Risk
No CV risk (no aspirin)	Traditional NSAID	COX-2 Specific NSAID *or* Traditional NSAID + PPI*
		Highest Risk: COX-2 + PPI
CV risk (consider aspirin)	Traditional NSAID± PPI* if degree of GI risk warrants gastroprotection	Consider non-NSAID therapy A PPI* must be added if a traditional NSAID is prescribed

*** Misoprostol can be substituted for a PPI**

Adapted from Fendrick AM, et al. *Pharmacy and Therapeutics* 2002; 27: 579. (ref 102)

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