Approaches to Nonsteroidal Anti-inflammatory Drug Use in the High-Risk Patient

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are probably the most common cause of gastroduodenal injury in the United States today. Approximately half of patients who regularly take NSAIDs have gastric erosions, and 15%–30% have ulcers when they are examined endoscopically. However, the incidence of clinical gastrointestinal (GI) events caused by NSAIDs is much lower. Clinical upper GI events may occur in 3%–4.5% of patients taking NSAIDs, and serious complicated events develop in approximately 1.5%. However, the risk varies widely in relationship to clinical features such as history of ulcers or GI events, age, concomitant anticoagulant or steroid use, and NSAID dose. This review discusses the risks of clinical GI disease in NSAID users, the predictors of increased risk, and strategies for prevention of NSAID-associated GI disease.

Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, are among the most widely used drugs in the world. There were approximately 111,400,000 NSAID prescriptions in the United States for the year ending in August 2000 at a cost of approximately $4,800,000,000.[1] One third of the total prescriptions and 60% of the cost were for cyclooxygenase (COX)-2–specific inhibitors.[1] In addition, annual U.S. sales of over-the-counter oral analgesics approach 3 billion dollars; NSAIDs (including aspirin) make up 60% of this market, and acetaminophen accounts for 40%.[2,3] The prevalence of at least once-weekly NSAID use among people 65 years old or older has been reported to be as high as 70%; half of this group takes at least 7 doses a week.[4]

NSAIDS are effective for the treatment of pain, inflammation, and fever, and aspirin is increasingly used for prophylaxis of vascular events. The main factor that limits the use of NSAIDs is their gastrointestinal (GI) toxicity.

Endoscopic Signs of Injury

A single dose of aspirin leads to gross gastric injury in the form of subepithelial hemorrhages within 15–30 minutes of ingestion.[5–7] Continued aspirin ingestion for 24 hours (650 mg 4 times a day) leads to the development of gastric erosions.[5,8] Virtually all subjects given aspirin develop these lesions in the first days of use.[5,8] However, subepithelial hemorrhages and erosions are mucosal lesions, whereas blood vessels of significant size are located in the submucosa or deeper. Thus, subepithelial hemorrhages and erosions do not cause major GI bleeding or lead to other complications such as perforation or obstruction.

Ulcers, which are generally defined in endoscopic studies as breaks in the mucosa $\geq$3 mm in diameter with unequivocal depth, may develop within 1 week of regular NSAID use. Combined data from studies in more than 900 volunteers showed an 8% incidence of ulcers after 7 days of standard NSAID or aspirin use.[9] Results from prospective, double-blind studies of NSAIDs yield widely variable results, but the cumulative incidence of gastroduodenal ulcers with use of traditional NSAIDs in recent studies has been as high as 25%–30% at 3 months[10–12] and 45% at 6 months.[10,11] The point prevalence of ulcers in patients taking NSAIDs regularly is approximately 15%–30%.[13]

The great majority of ulcers identified endoscopically do not cause clinical problems. Thus, the most relevant issue for NSAID users and their physicians is the development of clinically important GI events, such as bleeding, obstruction, and perforation.

Risk of Clinical Events

Only a small proportion of NSAID users develop GI complications. However, given the exceptionally widespread use of NSAIDs and aspirin, this small proportion translates into a large absolute number of NSAID users developing clinical GI events. A variety of epidemiologic studies (cohort and case-control) show a

Abbreviations used in this paper: 95% CI, 95% confidence interval; COX, cyclooxygenase; GI, gastrointestinal; OR, odds ratio; RR, relative risk.

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significant increase in clinical upper GI events with NSAID use (aspirin and nonaspirin NSAIDs), with most reports suggesting a 2–6-fold increase over the incidence in people not taking NSAIDs. However, when low-incidence outcomes such as NSAID-induced GI complications are assessed, absolute event rates may provide more clinically meaningful information than the frequently reported relative risk (RR) or odds ratio (OR).

Cohort studies in which data are available for a large group of people followed up over time (e.g., governmental database of an entire region's population, Medicaid or other payer database, patient registry) may be used to determine the rate of clinical GI events. Table 1 provides data on rates from 4 different cohort studies.[14–17] The excess annual risk of clinical GI events appears to range from approximately 0.2% to 1.25%, depending on definitions of GI events and patient factors such as age and comorbidities. Much less information is available on excess GI mortality with NSAID use. A rheumatoid arthritis patient registry (ARAMIS) had an annual mortality of 0.05% without NSAIDs and 0.22% with NSAID use.[17] Other groups of patients might have a lower NSAID-related excess mortality than the 0.17% seen in higher-risk patients with rheumatoid arthritis. A case-control study of mortality in a Tennessee Medicaid population aged ≥60 years reported an adjusted OR of 4.7 (95% confidence interval [95% CI], 3.1–7.2) with receipt of an NSAID prescription.[18]

Prospective experimental outcome studies may provide more precise estimates of the rate of NSAID-associated GI clinical events. Three large randomized, double-blind outcome studies have been performed in arthritis patients taking NSAIDs (Table 2).[19–21] Results from these trials indicate that clinically important upper GI events occur annually in 3%–4.5% of arthritis patients taking NSAIDs: 1.5% have serious complications (perforation, obstruction, or major bleeding), and the rest have either minor bleeding episodes or ulcers discovered when a GI work-up is initiated for severe or persistent symptoms.

NSAIDs may also cause an increase in clinical events beyond the duodenum. In the ARAMIS data bank, 13% of GI hospitalizations in patients with rheumatoid arthritis taking NSAIDs were for lower GI events, and 32% of GI hospitalizations in patients with osteoarthritis were for lower GI events.[17]

Risk of Clinical Events With Aspirin Vascular Prophylaxis

Aspirin is increasingly being used for vascular prophylaxis, so the risk of GI events in this group also must be assessed. Although many large-scale studies of aspirin prophylaxis have been performed, careful attention to GI events generally is not a primary aim of the studies. Results from 2 double-blind, placebo-controlled trials provide perhaps the best information on the increased risk with aspirin use. The Aspirin Myocardial Infarction Study included 4524 patients who received aspirin, 500 mg twice daily, or placebo for at least 3 years.[22] The proportion of patients hospitalized for ulcer disease was 1.4% in the aspirin group and 0.2% in the placebo group (adjusted RR, 9.5; 95% CI, 2.9–31.1). Because patients with a recent ulcer or history of a bleeding ulcer were excluded, the rates may underestimate the rate of aspirin-induced GI events. The U.K. TIA study included 2435 patients receiving placebo or aspirin, 300 mg or 1200 mg daily, for up to 7 years.[23] The rates of hospitalization for upper GI bleeding were 0.2%, 0.9% (OR, 3.6; 95% CI, 0.7–17.2), and 2.1% (OR, 8.7; 2.0–37.6). A recent cohort study of 903 patients discharged from a cardiology service on "low-dose" aspirin found an annual rate of hospitalization for upper GI bleeding of 1.2%.[24] Concomitant nonaspirin NSAID use was the main independent risk factor associated with an increased chance of bleeding (OR, 5.8; 95% CI, 1.8–19.2).

Doses of 75 mg of aspirin daily have been reported to significantly increase the risk of upper GI bleeding, with an OR of 2.3 (95% CI, 1.2–4.4) in a case-control study.[25] Even 10 mg of aspirin daily significantly inhib-

Table 1. GI Hospitalization Rates With and Without NSAID Use in Selected Large Population Cohorts

	Persons observed		Annual GI hospitalization rate		
Population studied	NSAID use	No NSAID use	GI event	NSAIDs	No NSAIDs
Tayside, Scotland > 50 yr[14]	52,293	73,792	Any upper GI event	1.29%	0.53%
			Complicated event	0.74%	0.23%
Odense, Denmark[15]	31,503	107,197	Ulcer/erosive bleeding	0.25%	0.05%
Tennessee Medicaid > 65 yr[16]	27,067 person-yr	134,560 person-yr	Upper GI bleeding or ulcer	1.67%	0.42%
ARAMIS Arthritis data bank[17]					
Osteoarthritis	2199 person-yr	1035 person-yr	Any GI event	0.73%	0.29%
Rheumatoid arthritis	8471 person-yr	3753 person-yr	Any GI event	1.46%	0.27%

Table 2. Prospective, Double-Blind GI Outcomes Studies in Arthritis Patients Taking NSAIDs

			Annualized incidence[b]			
	Therapies used		Clinical upper GI events[c]		Complicated upper GI events[d]	
Study[a]	NSAID control	Study drugs	Control	Study drug	Control	Study drug
MUCOSA[19]	10 NSAIDs (N = 4439)	Misoprostol 200 μg qid + NSAID (N = 4404)	3.1%	1.6%	1.5%	0.7%
CLASS[20]	Ibuprofen 800 mg tid, diclofenac 75 mg bid (N = 3987)	Celecoxib 400 mg bid (N = 3995)	3.5%	2.1%	1.5%	0.8%
			(No aspirin[e]: 2.9%	1.4%	1.3%	0.4%)
VIGOR[21]	Naproxen 500 mg bid (N = 4047)	Rofecoxib 50 mg qd (N = 4029)	4.5%	2.1%	1.4%	0.6%

NOTE. All differences between controls and study drugs were significant except clinical upper GI events in overall CLASS study ($P = 0.09$). qd, once daily; bid, 2 times daily; tid, 3 times daily; qid, 4 times daily.

[a]MUCOSA and VIGOR trials included only rheumatoid arthritis patients; CLASS trial included osteoarthritis (73%) and rheumatoid arthritis (27%).

[b]Incidence for MUCOSA trial represents doubling of results provided at 6 months (although median follow-up was <6 months). Incidences for VIGOR and CLASS trials represent rates per 100 patient-years, although VIGOR median follow-up was 9 months and CLASS data include only the first 6 months of the study.

[c]Includes perforations, obstructions, bleeding, and uncomplicated ulcers discovered on clinically indicated work-up.

[d]Includes perforation, obstruction, bleeding (documented due to ulcer or erosions in MUCOSA and CLASS; major bleeding in VIGOR).

[e]21% of patients in CLASS study were taking low-dose aspirin.

its gastric mucosal prostaglandin production, to levels similar to the inhibition with 81 and 325 mg of aspirin.[26] Thus, any dose of aspirin has the potential to cause upper GI events. Furthermore, the use of enteric-coated or buffered aspirin does not decrease the risk of major upper GI bleeding compared with plain aspirin at doses of ≤325 mg daily.[27] Because the primary mechanism by which aspirin and other NSAIDs induce GI complications is systemic rather than topical, it is not surprising that enteric-coated aspirin fails to decrease bleeding episodes.

Risk Factors for NSAID-Associated GI Events

A variety of clinical factors have been reported to significantly increase the risk of developing NSAID-associated GI events. Important factors that are validated in multiple studies include history of ulcer or GI complications, increasing age, concomitant anticoagulation therapy, concomitant corticosteroid use, and high-dose NSAID use.

History of Ulcers or GI Events

A history of ulcers or GI events may be the most important risk factor for future events. In the MUCOSA trial, multivariate analysis showed ORs for the development of a GI complication of 2.3 (95% CI, 1.3–4.1) for patients with a history of peptic ulcer and 2.6 (95% CI, 1.3–5.0) for patients with a history of GI bleeding[19] compared with patients without these prior events. A meta-analysis of 10 case-control or cohort studies indicated an OR of 4.8 (95% CI, 4.1–5.6) for patients with a prior (or unspecified) history of a GI event.[28] It should be noted that a history of ulcer or ulcer complications will significantly increase the risk of future GI events in all patients, whether or not they take NSAIDs. For example, in a large case-control study, the risk associated with past ulcer and no NSAID use was similar to the risk of NSAID use and no past ulcer (RR, 6), whereas the presence of both NSAID use and past ulcer increased the RR to 12.5.[29]

Age

Most studies document that the risk of NSAID-associated GI complications increases with age. The MUCOSA trial multivariate analysis indicated an OR of 2.5 (95% CI, 1.5–4.1) for patients ≥75 years old compared with younger patients.[19] A meta-analysis of 8 case-control studies indicated that NSAID use in patients ≥60 years old is associated with an OR of 5.5 (95% CI, 4.6–6.6) for GI events, whereas a review of 3 case-control studies showed an OR of 1.7 (95% CI, 1.1–2.5) for NSAID users younger than 60 years.[28] The age at which the risk of NSAID-associated GI events begins to increase significantly is uncertain. Using age 20–34 years as a reference, Lanza et al.[30] reported no significant increase in ulcer bleeding among patients aged 35–49 years who had received NSAID prescriptions during a 3-year study period but a 2.9-fold increase in patients aged 50–64 years (95% CI, 1.8–4.8). Older age itself is a risk factor for GI events. For example, a case-control study showed adjusted ORs for ulcer complications of

8.9 (95% CI, 4.3–18.3) before NSAID therapy in patients older than 75 years and 12.7 (95% CI, 5.5–29.4) in NSAID users older than 75 years.[31]

Anticoagulation

Concurrent use of oral anticoagulants was reported to increase the risk of hospitalization for bleeding ulcer in NSAID users ≥65 years old 12.7 times (95% CI, 6.3–25.7) in a Tennessee Medicaid population, whereas the risk in NSAID users not taking anticoagulants was 4.0 (95% CI, 3.4–4.8).[32]

Corticosteroids

Although corticosteroid use alone may not increase the risk of ulcer or ulcer complications, the use of steroids with NSAIDs does appear to increase the risk of GI events. Piper et al.[33] reported RRs of hospitalization for ulcer or upper GI bleeding of 1.1 (95% CI, 0.5–2.1) for steroid users (vs. nonusers) and 4.4 (95% CI, 2.0–9.7) for patients using NSAIDs and steroids (vs. NSAIDs alone). A meta-analysis of 3 studies reported an OR of 1.8 (95% CI, 1.2–2.8) for steroid use compared with no steroid use in NSAID users.[28]

Increasing Dose of NSAIDs

A number of studies have clearly documented that the risk of upper GI complications increases with increasing doses of NSAIDs.[17,29,34,35] The increase appears to be relatively linear. For example, the adjusted rate of ulcer hospitalizations per patient-year among Tennessee Medicaid patients ≥65 years old was 1.0% for low dose, 1.7% for moderate dose, and 2.2% for high dose.[16]

Severity of Rheumatoid Arthritis

The severity of rheumatoid arthritis disability also may be associated with some increase in risk of NSAID-associated GI events. A follow-up multivariate analysis of the MUCOSA trial reported that rheumatoid arthritis disability (measured by a modified Health Assessment Questionnaire) was an independent risk factor, although the magnitude of the increased risk was not provided.[36] A multivariate analysis from the ARAMIS data bank of patients with rheumatoid arthritis reported that disability (measured by Health Assessment Questionnaire score) was a risk factor for GI hospitalizations or deaths (OR, 1.3; 95% CI, 1.03–1.7).[17]

Heart Disease and Other Comorbidities

Other concurrent illnesses, such as heart disease, also may increase the risk of NSAID-associated GI events, although supportive data are limited. A multivariate analysis from the MUCOSA trial suggested a modest increase with heart disease (OR, 1.8; 95% CI, 1.1–3.2),[19] but apparently not with other comorbid diseases.[36] Weil et al.[37] reported that both heart failure and diabetes showed multiplicative effects with NSAID use for the development of ulcer bleeding, although quantification was not provided.[37] Certainly, the presence of comorbidities in patients who develop complications such as GI bleeding will significantly increase the risk of death due to the complication.[38]

Duration of NSAID Exposure

Conflicting results have been reported on the relationship of the risk of GI events to the duration of exposure to NSAIDs. A number of epidemiologic studies have suggested that the risk of GI complications is highest in the first month of NSAID use.[18,28,31,34,35] For example, a meta-analysis reported an OR of 8.0 (95% CI, 6.4–10.1) for <1 month of NSAID use, compared with 3.3 (95% CI, 2.3–4.8) for 1–3 months of use and 1.9 (95% CI, 1.2–3.1) for >3 months of use.[28] However, prospective experimental studies suggest a steady increase in the rate of GI complications over time. Survival curves showing time to ulcer hospitalization in the Aspirin Myocardial Infarction Study[22] and time to clinical upper GI event and time to complicated upper GI event in the VIGOR study[21] fail to show a drop-off in risk over time. These differences may be explained by the fact that patients who have not been taking NSAIDs appear to have an increased risk of developing ulcers and clinical events after starting NSAID therapy compared with those who have already been taking NSAIDs.

Dyspepsia

Upper GI symptoms are not good predictors of the development of upper GI events. Dyspepsia is extremely common in NSAID users. Larkai et al.[39] studied 245 rheumatic patients taking NSAIDs and reported that 16% had daily dyspepsia, 29% had symptoms in the prior week, and 37% had symptoms in the preceding 2 months. However, dyspepsia is extremely common even in patients not taking NSAIDs, so comparison with a control group not taking NSAIDs is necessary to determine the increase in risk. Using a validated questionnaire, Talley et al.[4] found that the use of NSAIDs doubled the risk of dyspepsia and heartburn in subjects ≥65 years of age.

Most patients with endoscopic lesions do not develop dyspepsia.[40,41] Larkai et al.[40] performed endoscopy on 65 patients regularly using NSAIDs and found that 4 (9%) of 41 with mucosal lesions had dyspepsia compared with 4 (19%) of 17 without mucosal lesions; 3 of 10 patients

with ulcers had dyspepsia. Furthermore, most NSAID users with GI complications have no antecedent symptoms.[42,43] However, others have reported that most patients not using NSAIDs who present with bleeding ulcers or erosions also have no symptoms (42 of 54 NSAID users vs. 33 of 40 non–NSAID users).[44]

Some investigators have suggested that dyspepsia is a risk factor for NSAID-associated GI complications. In a multivariate analysis of patients taking NSAIDs, Hansen et al.[31] reported that dyspepsia had a borderline significant 2-fold increase in risk for ulcer complications (OR, 2.0; 95% CI, 1.0–4.2); they also indicated that NSAID-related dyspepsia increased the OR to 8.7 (95% CI, 4.0–18.9), although the distinction between dyspepsia and NSAID-related dyspepsia was not defined. A multivariate analysis from the ARAMIS data bank of patients with rheumatoid arthritis reported that previous adverse GI effects of NSAIDs was a risk factor for GI hospitalization or death (OR, 1.6; 95% CI, 1.03–2.4).[17] However, a report providing raw data from the ARAMIS data bank on the incidence of GI hospitalizations related to GI side effects reported no significant association (no adverse effects, 2.1% incidence; adverse effects, 2.8% incidence; $P = 0.51$).[45] A multivariate analysis of the MUCOSA trial also indicated that concurrent use of antacids was a predictor of GI complications, although no quantification of risk was provided.[36]

Helicobacter pylori

Controversy exists regarding the interaction of *H. pylori* infection and NSAID use. *H. pylori* and NSAIDs are independent risk factors for the development of ulcers, but whether underlying *H. pylori* infection potentiates (or mitigates) the development of ulcers and clinical events is controversial. Most prospective endoscopic trials indicate that *H. pylori* does not increase the risk of developing GI tract injury (including ulcers) in patients taking NSAIDs.

However, in 1997, Chan et al.[46] reported that patients not using NSAIDs who were randomly assigned to receive bismuth triple therapy for *H. pylori* before they began taking naproxen had significantly fewer ulcers at 8-week endoscopy than patients not receiving *H. pylori* therapy before taking NSAIDs. In contrast, a double-blind European trial of *H. pylori* therapy in NSAID users indicated that healing of gastric ulcers (but not duodenal ulcers) was decreased with *H. pylori* therapy and that development of new ulcers over 6 months was comparable in the treatment and control groups.[47]

Chan et al.[48,49] subsequently evaluated the benefit of *H. pylori* therapy in *H. pylori*–positive patients using NSAIDs or low-dose aspirin who presented with bleeding ulcers. In this clinically important group, no benefit was identified in ulcer healing, and 6-month recurrent bleeding in naproxen users was significantly more common with *H. pylori* therapy than with omeprazole maintenance therapy (17% vs. 4%). In patients taking low-dose aspirin, the rate of recurrent bleeding was low and comparable in the 2 study groups at 1%–2%.[49]

Several case-control studies have been performed to assess the interaction of *H. pylori* and NSAID use in ulcer bleeding. Although Aalykke et al.[50] reported a borderline significant increase in *H. pylori* infection among NSAID users with ulcer bleeding (OR, 1.8; 95% CI, 1.0–3.2),[50] other studies do not show a significant increase in bleeding with *H. pylori* infection.[51–54] Some studies suggest a possible protective effect of *H. pylori* in ulcer bleeding, especially gastric ulcer bleeding.[51,53,54] A case-control study including only patients taking low-dose aspirin showed that *H. pylori* was a significant risk factor (OR, 5; 95% CI, 1.6–15.4).[55]

In summary, the weight of evidence does not suggest that *H. pylori* infection potentiates the risk of ulcer formation in NSAID users. Some data even suggest that *H. pylori* may be protective against gastric ulcer disease. However, *H. pylori* infection may potentiate the effect of low-dose aspirin with respect to ulcer bleeding. Certainly, both NSAID use and *H. pylori* infection are independent risk factors for ulcer disease. Therefore, in any individual ulcer patient one cannot be certain which factor is responsible for the ulcer, and both risks should be removed if possible.

Risks With Individual NSAIDs

NSAIDs inhibit prostaglandin production by inhibiting COX. Two isoforms of the COX enzyme are known to be involved in prostaglandin synthesis. COX-1 is constitutively expressed and generates prostaglandins involved in GI mucosal protection and platelet function, whereas COX-2 is induced at sites of inflammation to generate prostaglandins that mediate inflammation and pain. The anti-inflammatory effects of nonselective NSAIDs appear to be mediated via COX-2 inhibition, whereas the harmful effects in the GI tract and platelets are believed to be caused primarily by COX-1 inhibition.

All traditional nonselective NSAIDs are associated with an increased risk of GI events, and the confidence intervals for the risks of individual NSAIDs generally overlap. In general, ibuprofen has the lowest risk among older NSAIDs, whereas piroxicam[28,56,57] and ketorolac[58] have the greatest risks. Lower daily doses of ibuprofen may explain its apparent relative safety; the risk approaches that of other traditional NSAIDs when used

at higher daily doses that are equipotent to other NSAIDs.[56]

Endoscopic studies suggest that 3 older NSAIDs cause less injury to the GI tract: nonacetylated salicylates, etodolac, and nabumetone. Studies of 1 week to 3 months report significantly less gastroduodenal damage with salsalate than with aspirin or naproxen; salsalate did not produce a significant decrease in mucosal prostaglandin content at 1 week.[59,60] Several endoscopic studies indicate that etodolac, which has some COX-2 selectivity, causes significantly less mucosal injury than traditional NSAIDs (naproxen, ibuprofen, indomethacin), again apparently because of a lack of significant decrease in mucosal prostaglandin production.[61,62] Finally, nabumetone also has been noted to cause significantly less endoscopic injury than other standard NSAIDs. In a large 6-week, placebo-controlled endoscopic trial, nabumetone (1500 mg daily) caused significantly fewer gastric or duodenal ulcers than naproxen (500 mg twice daily; 11% vs. 37%) but significantly more than placebo (11% vs. 5%).[63] No large-scale studies are available to document that the decrease in endoscopic injury translates into a decrease in clinical events, although post hoc analyses suggest that nabumetone and perhaps etodolac induce fewer GI complications.[64,65]

Meloxicam is a new NSAID recently approved in the United States. This agent is relatively COX-2 selective. The major data regarding GI safety come from 2 large 4-week double-blind trials comparing lower-dose meloxicam (7.5 mg daily) with diclofenac, 100 mg daily, or with piroxicam, 20 mg daily. The diclofenac trial of 9323 patients with osteoarthritis showed clinical upper GI events in 5 patients taking meloxicam and 7 taking diclofenac.[66] The piroxicam study of 8656 patients with osteoarthritis had clinical upper GI events in 7 patients taking meloxicam and 16 patients taking piroxicam.[67] Although these differences were not significant, a meta-analysis suggested a decrease in reported clinical GI events with meloxicam.[68]

Strategies to Decrease NSAID-Associated GI Events

Several strategies may be used to decrease the risk of NSAID-associated GI events. First, GI complications can be avoided by the use of non-NSAID analgesics, when possible. Second, use of the lowest effective dose of an NSAID will decrease the chance of complications. Third, medical cotherapy can be used in patients with increased risk of complications. Finally, the development of less injurious NSAIDs such as the COX-2–specific inhibitors will decrease the risk of GI events.

Cotherapy

Placebo-controlled, double-blind trials show that H_2-receptor antagonists, when given for 8 weeks at standard doses, prevent NSAID-associated duodenal ulcers but not gastric ulcers.[69,70] It appears that prevention of gastric ulcers requires greater degrees of acid inhibition. Double-dose famotidine (40 mg twice daily) significantly decreased gastric ulcers compared with placebo (20% vs. 8%) in a 24-week double-blind trial.[71] However, standard-dose proton pump inhibitor therapy has significantly fewer gastric and duodenal ulcer recurrences than standard-dose H_2-receptor antagonist in NSAID users[72] (Figure 1*A*) and is the antisecretory therapy of choice to prevent NSAID ulcers.

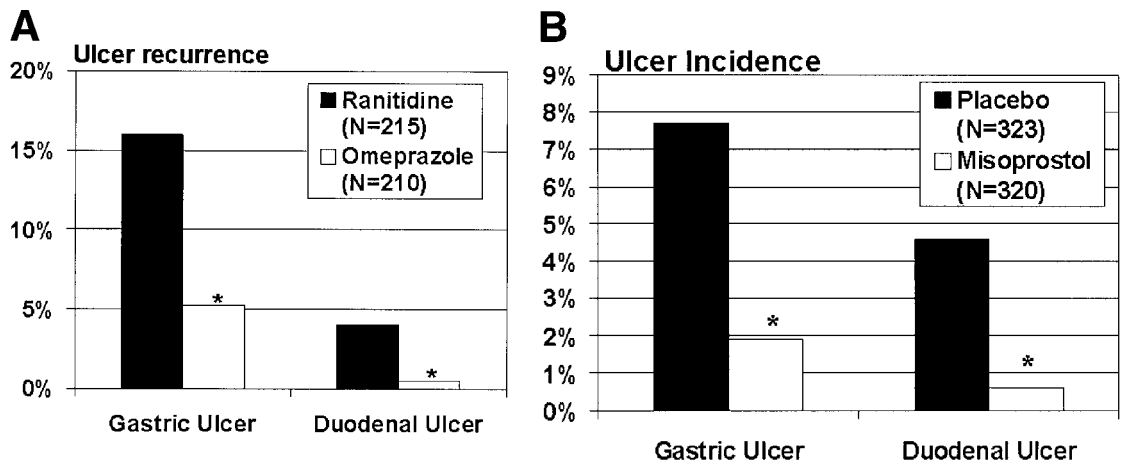

Figure 1. Double-blind endoscopic trials of medical cotherapies for prevention of NSAID-induced ulcers. (*A*) Six-month trial of ranitidine, 150 mg twice daily, vs. omeprazole, 20 mg daily, in NSAID users with recent ulcer or >10 erosions.[72] (*B*) Twelve-week trial of misoprostol, 200 μg 4 times daily, vs. placebo in arthritis patients without recent ulcer.[73] $*P < 0.05$.

Misoprostol, a synthetic prostaglandin E_1 analogue, also significantly reduces the development of both gastric and duodenal ulcers in placebo-controlled double-blind trials[73] (Figure 1*B*). Misoprostol is associated with an increased risk of GI symptoms and discontinuations because of GI symptoms, especially when given 4 times a day. The most important symptom is diarrhea, although symptoms such as abdominal pain, nausea, and flatulence may also be increased.[73,74] Raskin et al.[74] reported that thrice-daily misoprostol administration was comparable to administration 4 times a day for prevention of both gastric and duodenal ulcers,[74] whereas studies of a combination of diclofenac (50 or 75 mg) and misoprostol, 200 μg (Arthrotec; Pharmacia, Peapack, NJ) show that twice-daily misoprostol is effective in preventing ulcer formation. A 6-week double-blind study of 334 patients receiving placebo and 368 receiving the combination twice daily showed no significant difference in the development of gastric ulcers (4% vs. 1%) or duodenal ulcers (1% vs. 4%).[63]

Direct comparisons of proton pump inhibitors and misoprostol suggest that proton pump inhibitors provide protection against NSAID ulcers at least comparable to those of misoprostol, with fewer GI symptoms. Hawkey et al.[75] found that omeprazole, 20 mg daily, was comparable to misoprostol, 200 μg twice daily, for prevention of gastric ulcers (13% vs. 10% over 6 months) but superior for duodenal ulcer prevention (3% vs. 10%), with fewer patients discontinuing treatment because of adverse events (4% vs. 8%). Rose et al.[76] showed similar rates of recurrent ulcers at 12 weeks with lansoprazole, 30 mg daily, and misoprostol, 200 μg 4 times daily, although misoprostol was associated with a significantly greater incidence of diarrhea (22% vs. 7%).

Thus, endoscopic studies suggest that misoprostol and proton pump inhibitors are both effective at preventing NSAID-associated ulcers. Proton pump inhibitors may be preferable due their once-daily dosing, their ability to decrease dyspeptic symptoms,[77] and their lower rate of GI side effects. However, the only study to assess the incidence of clinical GI events with any of these agents was performed with misoprostol, 200 μg 4 times daily.[19] The MUCOSA trial compared misoprostol with placebo in 8843 patients with rheumatoid arthritis who were taking NSAIDs for up to 6 months (Table 2). Based on an estimate of annualized incidences (doubling of the incidences for the 2 study groups), the number needed to treat with misoprostol to avert 1 ulcer complication at 1 year is 132. The RR reduction in ulcer complications of 51% over 6 months in the MUCOSA trial is similar to the 58% RR reduction reported in the incidence of gastroduodenal ulcers in a 6-month endoscopic study.[78] Although the results of the MUCOSA trial suggest that endoscopic ulcer trials are likely to be predictive of GI outcome trials, misoprostol is the only cotherapy that has been documented to decrease the risk of NSAID-associated clinical GI events.

COX-2–Specific Inhibitors (Coxibs)

COX-2 selectivity of different agents can be measured by assays of prostaglandin production in whole blood. The ratio of the concentrations producing 50% inhibition (IC_{50}) of COX-1 and COX-2 provides a measure of selectivity, with higher numbers indicating greater selectivity for COX-2 (greater sparing of COX-1). Chan et al.[79] reported values of 36 for rofecoxib, 7 for celecoxib, 3 for diclofenac, 2 for meloxicam, and 0.4 for indomethacin. A more clinically relevant way to look at COX-2 selectivity is to ask, when an NSAID is used at therapeutic or supratherapeutic doses, how much it will inhibit COX-1 or at how high a dose COX-1 inhibition will begin to occur. COX-2–specific inhibitors (also called coxibs) produce little if any COX-1 inhibition, even at doses markedly above the therapeutic range. For example, celecoxib at 400 mg[80] and rofecoxib at 1000 mg[81] fail to cause inhibition of COX-1 activity.

Certainly, caution must be exercised in attempting to translate in vitro and ex vivo studies to the clinical setting. Large clinical trials of the 2 recently approved coxibs, celecoxib and rofecoxib, provide an excellent opportunity to determine if the theoretical benefit of COX-2 selectivity translates in clinical practice.

Double-blind endoscopic studies in patients with arthritis indicate that celecoxib and rofecoxib cause significantly fewer ulcers than nonselective NSAIDs over 6 months, with rates comparable to placebo over 3 months[10–12,82] (Figure 2). In addition, 2 double-blind GI outcome studies,[20,21] each consisting of approximately 8000 patients, showed significantly lower rates of clinically relevant GI outcomes with coxibs than with traditional NSAIDs (Table 2). The RR reductions in clinical upper GI events and in complicated events were ~50%–65%. The number of patients needed to treat with a coxib instead of a traditional NSAID to prevent 1 clinical upper GI event in a year was ~40–65, and the number needed to prevent a complicated event was 120–125. Rofecoxib significantly decreased bleeding episodes both from gastroduodenal sites and from sites beyond the upper GI tract.[21] Thus, we have strong evidence that COX-2–specific inhibitors decrease not only endoscopically visualized ulcers, but also clinically important GI events.

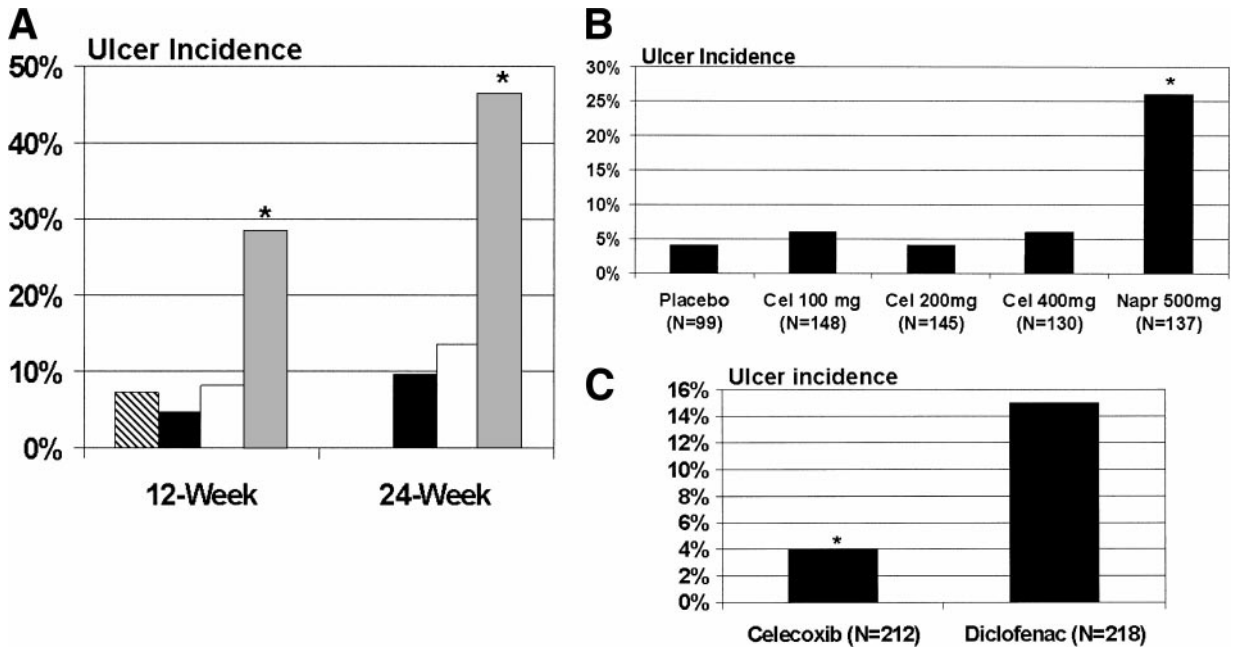

Figure 2. Double-blind endoscopic trials of coxibs in patients with arthritis. (*A*) Combined results from 2 identical 24-week studies (placebo for 16 weeks) of placebo (▨, n = 340); rofecoxib, 25 mg (■, n= 373) or 50 mg (□, n = 360) daily; or ibuprofen, 800 mg 3 times daily (▩ , n = 354) in patients with osteoarthritis.[10,11] $*P < 0.001$ vs. placebo, rofecoxib 25 and 50 mg. (*B*) 12-Week trial of placebo; celecoxib, 100, 200, or 400 mg twice daily; or naproxen, 500 mg twice daily, in patients with rheumatoid arthritis.[12] $*P < 0.01$ vs. other groups. (*C*) 24-Week trial of celecoxib, 200 mg twice daily, or diclofenac, 75 mg twice daily, in patients with rheumatoid arthritis.[82] $*P < 0.001$.

Economic Considerations

Economic considerations are key in determining management of the GI risk in patients taking NSAIDs. The cost of NSAID-associated GI side effects is substantial. For example, using the Quebec health insurance database for 1993–1997, Rahme et al.[83] estimated that for each dollar spent on NSAIDs, $0.66 is spent on their GI side effects. Using Medicaid data from Washington, D.C., for 1981–1983, Bloom[84] found that 31% of the total cost of care for "arthritis" patients was for management of GI adverse events. Medications accounted for 42% of the cost for adverse GI effects, hospitalization for 38%, and physician or clinic expenses for 20%. Smalley et al.[85] examined all 1989 Tennessee Medicaid enrollees ≥65 years old and reported that $111 per patient was spent annually for management of GI disorders in regular NSAID users: $55 on hospitalizations, $48 on medication prescriptions, and $8 on outpatient visits.

In contrast, Lanes et al.,[86] assessing costs from a Massachusetts health maintenance organization in 1993–1994, found that GI medications accounted for most of the GI-related costs in patients with rheumatoid arthritis and osteoarthritis (NSAID use was not a requirement for inclusion in this study). Annual costs for antiulcer medications were $211 for patients with rheumatoid arthritis and $80 for patients with osteoarthritis, whereas hospital admissions for GI symptoms accounted for only $16 per year. The annual costs of NSAIDs were $427 in the rheumatoid arthritis group and $79 in the osteoarthritis group.

Thus, economic analyses suggest that NSAID-associated adverse GI effects markedly increase health care costs. Medications given to prevent GI events or to treat dyspsepsia may represent the greatest cost, although the infrequent but expensive hospitalizations for GI complications also contribute to the economic burden.

If cost were not an issue, all patients would receive COX-2–specific inhibitors and/or cotherapy with agents such as proton pump inhibitors. However, economic assessments of the impact of therapies are needed to help determine management strategies. Cost-effectiveness analyses provide a cost per clinical outcome: e.g., cost per year of life saved, cost per GI complication averted. To evaluate a safer but more expensive therapy (e.g., cotherapy, coxibs), the overall cost of managing the disease state over time must be assessed, and 3 economic outcomes are possible. First, a therapy may be cost saving if the overall cost of care is decreased. This would occur if the greater cost of a therapy was more than offset by a decrease in costs attributable to decreased hospitalizations and/or comedications. Second, a therapy may increase the overall costs of care but be considered cost-effective, i.e., the increase in cost to prevent a clinical event or death is considered acceptable to society or

payers. Third, a therapy may increase the overall cost of care more than is acceptable, and the therapy would not be considered cost-effective.

Economic analyses of the utility of misoprostol prophylaxis have yielded wildly divergent results. A recent analysis using the actual data from the MUCOSA trial, with cost estimates from the Ontario, Canada, health care plan, reported that averting 1 serious GI complication would cost an additional $94,766 Canadian.[87] The cost was decreased to $14,943 Canadian in patients with previous peptic ulcer disease and only $4101 Canadian for patients ≥75 years old with previous ulcer disease. Thus, cotherapy is cost-effective in patients with high-risk clinical features.

Economic Analysis of COX-2–Specific Inhibitors

Cost considerations play a major role in deciding which patients should receive the new COX-2–specific inhibitors. Using wholesale medication costs from our university hospital pharmacy buying consortium (which provides lower and more realistic prices than the commonly used average wholesale price), Medicare reimbursements for endoscopy, doctor visits, laboratory testing, and GI bleeding hospitalization, and estimates from clinical trials.[20,21,88–90] Table 3 presents a rough economic analysis for replacing a generic NSAID with a coxib in a hypothetical cohort of 1000 arthritis patients using NSAIDs for 1 year. The cost of averting 1 clinical upper GI event in this hypothetical cohort would be $28,186 ($667,950–$104,236/20 clinical events), and the cost per complicated event averted would be $66,319 ($667,950–$104,236/8.5 complicated events).

Although the assumptions in this analysis can be questioned and costs will vary, sensitivity analyses clearly show that in addition to the cost of coxibs, only 2 variables can markedly influence the results: the number of GI events requiring hospitalization and the proportion of patients taking proton pump inhibitors or misoprostol.

As the risk of complicated events and hospitalizations increases (e.g., older age, history of GI events), the cost per event averted decreases. In this analysis, when the absolute risk reduction of hospitalizations for complicated events reaches 10.6%, the use of coxibs becomes cost saving. This absolute risk reduction is exceeded in patients ≥65 years old with a history of a clinical GI event (Laine L, unpublished data).

As the number of patients taking cotherapy with proton pump inhibitors or misoprostol increases, the cost per event averted decreases. A coxib is cost saving compared with a traditional NSAID plus a proton pump inhibitor, misoprostol (200 μg thrice daily or 4 times daily), or Arthrotec 75 twice daily, assuming coxibs provide at least equal GI safety. In this analysis, if 48.3% of patients are taking a proton pump inhibitor with a traditional NSAID, a switch to a coxib without cotherapy would be cost saving. However, many patients may still use a proton pump inhibitor even after changing to a coxib (e.g., dyspepsia, reflux symptoms, history of GI events), so we cannot assume that every patient making the switch to a coxib will discontinue taking proton pump inhibitors.

Table 3. Economic Analysis of COX-2–Specific Inhibitor (Coxib) in Place of Generic NSAID in a Cohort of 1000 Arthritis Patients Taking NSAIDs for 1 Year

Increase in cost with coxib:	**$667,950**
Medication cost:	$667,950
$1.95 (rofecoxib 25 mg qd) − $0.12 (naproxen 500 mg bid)	
Decreases in cost with coxib:	**$104,236**
Decrease in hospitalization for GI complication:	$ 42,614
0.8%: ($5326.77 per bleeding hospitalization)	
Decrease in GI comedications:	$ 45,041
7%: (3%: proton pump inhibitor [$3.20 qd]; 3%: H_2-receptor antagonist [$0.10 qd] 1%: misoprostol/Arthrotec 75 [$2.44 qd])	
Decrease in outpatient GI procedures:	$ 8200
1.5%: upper endoscopy ($546.68 per procedure)	
Decrease in outpatient visits:	$ 8381
2%: GI consultations ($138.19)	
4%: Primary care follow-ups ($58.22)	
6%: Associated laboratory tests, fecal occult blood test ($54.81)	

qd, once daily; bid, 2 times daily.

Summary and Recommendations

Endoscopic ulcers are found in ~15%–30% of patients who take NSAIDs regularly, but clinical GI events are relatively infrequent. Prospective outcome studies indicate an annual incidence of complicated GI events (perforation, obstruction, major bleeding) in arthritis patients of ~1.5% and an annual rate of all clinical GI events (complicated events plus ulcers discovered on work-up for significant GI symptoms) of ~3%–4.5%. Population cohort studies suggest that the annual rate of excess GI hospitalization for upper GI bleeding or for GI complications related to NSAID use is in the range of 0.25%–1.25%.

Important factors that have been shown to increase the risk of NSAID-associated GI complications in multiple studies include history of ulcer or GI complications, increasing age, concomitant anticoagulation therapy, concomitant corticosteroid use, and high-dose NSAID use. Other factors that may increase risk include severity

of rheumatoid arthritis and heart disease or other comorbidities. Dyspepsia is extremely common and correlates poorly with NSAID-associated ulcers or complications; however, some have suggested that dyspepsia may also be associated with an increased risk of GI complications. Current evidence does not support the concept that *H. pylori* potentiates the risk of NSAID-induced GI ulcers or clinical events, and a strategy of *H. pylori* testing and treatment in NSAID users without a history of ulcer disease is not recommended.

The use of low-dose aspirin for vascular prophylaxis significantly increases the risk of upper GI bleeding. Enteric-coated or buffered aspirin does not appear to decrease this risk. Concomitant NSAID use is an important risk factor for the development of bleeding in patients taking low-dose aspirin. Limited evidence suggests that *H. pylori* may be important in potentiating the development of low-dose aspirin–induced upper GI bleeding.

A variety of strategies may be used to decrease the risk of NSAID-associated GI events (Table 4). First, the use of non-NSAID analgesics when possible will prevent the development of NSAID-related GI events. Second, use of the lowest effective dose of an NSAID decreases the risk of GI complications. Third, when traditional NSAIDs are used, generic agents with potentially lower risk (etodolac or nonacetylated salicylates) should be considered. Fourth, medical cotherapy may be used. Although H_2-receptor antagonists may decrease dyspepsia, they are not effective at standard doses in decreasing the risk of gastric ulcers and should not be used for prophylaxis. Proton pump inhibitors administered once a day and misoprostol, 200 μg 2–4 times daily, have been shown to significantly decrease gastric and duodenal ulcers in endoscopic studies. Comparative endoscopic studies suggest that proton pump inhibitors have similar efficacy with fewer side effects than misoprostol. However, misoprostol (at a dose of 200 μg 4 times daily) is the only cotherapy that has been documented to decrease clinical GI events.

Finally, the use of COX-2–specific inhibitors significantly decreases the rate of endoscopic ulcers compared with traditional NSAIDs, with rates comparable to placebo. Prospective GI outcome studies also indicate that these agents significantly decrease complicated upper GI events and all clinical GI events compared with traditional NSAIDs. The number of patients who need to be treated in 1 year to avert 1 clinical event is 40–65 and to avert 1 complicated event is 120–125.

Although coxibs are significantly safer than traditional NSAIDs, they are also much more expensive. Currently, the cost that is considered acceptable to society to prevent a GI clinical event is not clear. It is clear that the cost-effectiveness of coxibs increases (i.e., the cost per GI event averted decreases) in higher-risk NSAID users. This is because patients with high-risk clinical features have higher rates of GI hospitalizations and greater use of expensive prophylactic cotherapy.

Thus, patients at low risk for GI clinical events probably will receive traditional, inexpensive generic NSAIDs, and patients with high-risk clinical features may be given COX-2–specific inhibitors. Patients with high-risk features who take aspirin for vascular prophylaxis should receive GI cotherapy. I generally use a proton pump inhibitor rather than misoprostol for reasons of compliance (once-daily administration) and adverse effect profile. Patients who have GI complications while taking a coxib, and possibly those with a history of a complication before the use of a coxib, also should receive cotherapy.

Table 4. Approaches to Decreasing Risk of Clinical GI Events in NSAID Users

Use non-NSAID analgesics if effective
Use lowest effective dose of NSAID
When using traditional NSAID, consider generic agents with potentially lower risk:
Etodolac
Nonacetylated salicylates
Use COX-2–specific inhibitor—largest risk reduction in patients with high-risk clinical features:
Prior ulcer or GI event
Older age (e.g., >65 years)
Anticoagulation therapy
Corticosteroid therapy
Low-dose aspirin therapy for vascular prophylaxis
Severe rheumatoid arthritis
Use GI cotherapy (proton pump inhibitor or misoprostol)
Patients taking traditional NSAID or low-dose aspirin with high-risk factors
Patient taking coxib with prior GI complication

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