Guidelines for Prevention of NSAID-Related Ulcer Complications

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Guidelines for clinical practice are intended to indicate preferred approaches to medical problems as established by scientifically valid research. Double-blind, placebo-controlled studies are preferable, but compassionate use reports and expert review articles are used in a thorough review of the literature conducted through Medline with the National Library of Medicine. Only when data that will not withstand objective scrutiny are available is a recommendation identified as a consensus of experts. Guidelines are applicable to all physicians who address the subject, without regard to specialty training or interests, and are intended to indicate the preferable, but not necessarily the only, acceptable approach to a specific problem. Guidelines are intended to be flexible and must be distinguished from standards of care, which are inflexible and rarely violated. Given the wide range of specifics in any health-care problem, the physician must always choose the course best suited to the individual patient and the variables in existence at the moment of decision. These guidelines were developed under the auspices of the American College of Gastroenterology by a committee of experts in the field, reviewed by its Practice Parameters Committee, and approved by the Board of Trustees. The recommendations of these guidelines are therefore considered valid at the time of production based on the data available. New developments in medical research and practice pertinent to each guideline will be reviewed at an established time and indicated at publication to assure continued validity. Owing to the volume of new data on the subject of non-steroidal anti-inflammatory drug (NSAID)-related injury to the upper gastrointestinal tract, i.e., the advent of cyclooxygenase (COX)-2 inhibitors, new data on interactions between these agents, as well as traditional NSAIDs, with aspirin and *H. pylori*, it was elected by the Committee to confine these guidelines to upper gastrointestinal (GI) injury and to leave post-duodenal injury as the subject of a separate guideline.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are valuable agents in the treatment of arthritis and other musculoskeletal disorders, and as analgesics in a wide variety of clinical scenarios. Unfortunately, their use has been limited by their association with mucosal injury to the upper gastrointestinal tract, including the development of peptic ulcer disease and its complications, most notably upper gastrointestinal hemorrhage, and perforation (1–2). As many as 25% of chronic NSAID users will develop ulcer disease (3–4) and 2–4% will bleed or perforate (5–6). These gastrointestinal events result in more than 100,000 hospital admissions annually in the United States and between 7,000 and 10,000 deaths, especially among those who have been designated as being in a high-risk category (7–9). In a large meta-analysis, the overall relative risk for these complications in patients taking NSAIDs was approximately 2.4 (10). However, this relative risk was markedly increased among patients who fall into various high-risk categories (10–12). Physicians prescribing NSAIDs are, therefore, presented with two problems: (i) identification of high-risk patients and (ii) the selection of appropriate strategies to prevent peptic ulcer and its complications. Concerns raised regarding potential cardiovascular (CV) hazards of cyclooxygenase (COX)-2 inhibitors and other NSAIDs have complicated clinical decision making further; in selecting an agent for the management of his or her patient, the physician

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must now balance not only analgesic and anti-inflammatory potency against gastrointestinal toxicity, but must also assess cardiovascular risk for the individual patient in relation to the widely contrasting cardiovascular effects of NSAID classes and individual agents. An additional factor added to this issue is the recognition that aspirin and NSAIDs, including Coxibs, may reduce the risk of colonic adenoma and colorectal cancer occurrence or recurrence; as a consequence, the risk/benefit for gastrointestinal (GI) and CV events for those on low-dose aspirin and NSAIDs in a theoretically healthy population now confronts us (13–14).

RISK FACTORS FOR NSAID-RELATED COMPLICATIONS

Risk factors for GI complications associated with NSAIDs have been identified through a series of case–control and cohort studies that compared outcomes for patients taking these agents with those of control groups. A series of nested case–control studies based on incidence rates for hospitalization for GI bleeding in Medicaid recipients above the age of 65 years in Tennessee showed an increased risk for those above the age of 65 years (odds ratio 4.7), those on higher doses of NSAIDs (odds ratio 8.0), those who had a relatively short-term history of NSAID use (less than 1 month; odds ratio 7.2), as well as those who were concurrently taking corticosteroids (odds ratio 4.4) or anticoagulants (odds ratio 12.7) (15–18). These findings have been confirmed in other individual studies. In a large series based on autopsy findings on patients with a history of NSAID use, gastric and duodenal ulcers were found to be more common among patients who had consumed NSAIDs for less than 3 months (19). Although the risk of ulcer complications decreases after the first few months of NSAID use, it does not vanish with long-term therapy. A large retrospective cohort study, also based on data from Medicaid patients, revealed a similar increased risk overall for GI bleeding in patients taking NSAIDs, especially for those over the age of 60 (20). Similar data have been obtained from other large cohort studies (21–22). A large prospective multicenter study in rheumatoid arthritis patients ($N = 2{,}747$) revealed that the principal risk factors for serious GI events and hospitalization were age, a history of prior NSAID-related ulceration and its complications, corticosteroid use, and debility. The overall incidence, in this particular study, for hospitalization for serious GI events and death during NSAID therapy in rheumatoid arthritis patients was 1.58% (12).

Another large prospective, double-blind, randomized controlled trial in over 8,000 patients with rheumatoid arthritis identified cardiovascular disease as a major risk factor for upper GI complications of NSAID use (odds ratio 1.84). In this same study, patients over the age of 75 (odds ratio 2.48), patients with prior peptic ulcer (odds ratio 2.29), and prior GI bleeding (odds ratio 2.56) were again associated with increased risk (23).

More recent studies suggest that the risk of GI complications may be lower with the use of NSAIDs, such as ibuprofen, nabumetone, meloxicam, and etodolac and higher with sulindac, piroxicam, and ketorolac (24–26). In the case of ibuprofen, this may be due to the use, in general, of lower analgesic doses, especially in relation to ibuprofen preparations that are available over the counter. Nabumetone, meloxicam, and etodolac may possess some degree of COX-2 selectivity whereas sulindac, piroxicam, and ketorolac may owe their increased toxicity to the presence of relatively long plasma half-lives, thereby, resulting in a more prolonged mucosal exposure (27).

A very large study from the Spanish National Health System revealed a death rate of 15.3 persons per 100,000 NSAID/aspirin users. The most interesting finding in this Spanish study is that the reported death rate associated with NSAID use was only one-third of the death rate widely quoted in the United States (28). The latter has been criticized on the basis that the NSAID-related mortality reported by Singh *et al.* (8) was extrapolated from a small sample of rheumatoid arthritis patients and that rheumatoid arthritis itself was associated with increased mortality, independent of NSAID use. Approximately 50% of the patients who died in the Spanish study had a prior history of one, or more, of the following risk factors: peptic ulceration (21.6%), GI bleeding (15.3%), dyspepsia (13.3%), cardiac disease (65.1%), or hypertension (40%). The average age of patients dying from NSAID/ASA complications was 70±13.5 years and 89.7% of those who died were above the age of 60 years (28).

The use of low-dose aspirin alone, in the absence of other risk factors is associated with an increased risk for both GI bleeding and death from GI complications (28). Numerous studies in patients taking low-dose aspirin alone have shown a relative risk of 2–4 for GI bleeding (29–35). A recent meta-analysis of 14 randomized controlled trials (RCTs), which included over 57,000 patients on low-dose aspirin (75–325 mg daily), revealed a relative risk of 2.07 for significant GI bleeding (33). Furthermore, a large percentage of patients on low-dose aspirin are elderly, have multiple co-morbidities, and cardiovascular disease, in particular, and are likely to be concurrently prescribed anticoagulants, NSAIDs and corticosteroids, any one of which will elevate their relative risk for GI events to several times that of low-dose aspirin alone (34–35). It is important to emphasize that physicians are often unaware that patients are self-medicating with low-dose aspirin when they are prescribed an NSAID for pain relief or anti-inflammatory effect.

Up until recently, the analysis of data on the role of *H. pylori* infection as a risk factor for GI bleeding in NSAID users was complicated by a failure, in many studies, to account for the variable influence of multiple, coexistent risk factors. Not surprisingly, therefore, several studies yielded conflicting results (36–37). To date, there are data to show that *H. pylori* increases, has no effect on, and decreases the risk of ulcer in NSAID users (38).

A comprehensive meta-analysis of 16 case–controlled studies demonstrated that the risk of peptic ulcer bleeding was increased by a factor of 1.79 with *H. pylori* infection, by 4.85

with NSAID usage and by 6.13 in the presence of both NSAID use and *H. pylori* infection, strongly suggesting an additive effect (39). An updated meta-analysis showed similar findings (40). Further support for an additive role for *H. pylori* infection in the context of NSAID use comes from trials of the impact of *H. pylori* eradication. Indeed, the eradication of *H. pylori* in high-risk patients prior to the initiation of NSAID therapy has been shown to significantly reduce the risk of subsequent ulceration (41–43). Two systematic reviews have consistently shown that eradication of *H. pylori* is superior to placebo in the primary prevention of peptic ulcers among NSAID users (risk ratio (95% CI) 0.35 (0.20–0.61)) (40,44). Using a Markov model, Leontiadis *et al.* (44) showed that the most cost-effective strategy for primary prevention of NSAID-associated ulcer was *H. pylori* eradication in patients above the age of 50 years. Interestingly, the sensitivity analysis showed that the eradication therapy remained cost-effective to *H. pylori* prevalence as low as 5%. As there is an influx of immigrants to the United States from countries with a high prevalence of *H. pylori* infection, eradication of *H. pylori* has the potential of being an effective and affordable strategy for primary prevention of NSAID-associated ulcer disease. However, many patients take NSAIDs intermittently and often for only short periods at a time. Whether a test and treat strategy would be cost effective for this large group is unknown. Furthermore, it has also been noted that eradication of *H. pylori* infection alone is not sufficient for the secondary prevention of peptic ulcer bleeding in chronic NSAID users (45–49). In one of these studies, 400 *H. pylori*-positive patients with a history of GI bleeding who had been taking 80 mg of aspirin ($N=250$), or a traditional NSAID ($N=150$), were treated with a proton pump inhibitor (PPI) for 8 weeks, and then placed on aspirin 80 mg a day, or naproxen 500 mg b.i.d. They were then randomized to receive 1 week of bismuth-based triple therapy to eradicate *H. pylori* followed by placebo for 6 months or a PPI (omeprazole 20 mg daily) for 6 months. In the low-dose aspirin group, there was no difference in the incidence of recurrent bleeding between the *H. pylori* eradication group and the group taking the PPI. In the patients receiving naproxen, PPI therapy was clearly superior to *H. pylori* eradication in preventing recurrent bleeding (14.4% absolute difference in probability of bleeding, 95% CI, 4.4–24.4%, $P=0.005$) (41). Another RCT showed that after *H. pylori* eradication, co-therapy with a PPI (lansoprazole 30 mg daily) significantly reduced the risk of rebleeding in high-risk patients taking low-dose aspirin when compared with those taking aspirin and placebo (1.6 vs. 14.8%, $P=0.008$). However, of the patients who re-bled in the placebo group, two-thirds had either failed to eradicate *H. pylori* or had used concomitant NSAIDs (45). Excluding these confounders, only 5% of patients with successful eradication of *H. pylori* had recurrent ulcer bleeding with low-dose aspirin in 12 months. Large-scale, long-term studies are required to evaluate the true benefit of *H. pylori* eradication in low-dose aspirin users who are at risk of ulcer complications. Why should the effect of *H. pylori* eradication be different between NSAID users and low-dose aspirin users? One likely explanation is that low-dose aspirin is not as ulcerogenic as NSAIDs. Thus, low-dose aspirin probably provokes bleeding in pre-existing *H. pylori* ulcers. Curing the infection heals *H. pylori* ulcers so that resumption of low-dose aspirin alone is not sufficient to induce recurrent ulceration.

Conclusions

(i) Risk factors for NSAID-related GI complications include a previous GI event, especially if complicated, age, concomitant use of anticoagulants, corticosteroids, other NSAIDs including low-dose aspirin, high-dose NSAID therapy, and chronic debilitating disorders, especially cardiovascular disease.

(ii) Low-dose aspirin is associated with a definite risk for GI complications.

(iii) *H. pylori* infection increases the risk of NSAID-related GI complications.

(iv) There is a potential advantage of testing for *H. pylori* infection and eradicating the infection if positive in patients requiring long-term NSAID therapy. Whether co-therapy with a gastroprotective agent is needed after eradication of *H. pylori* depends on individual patients' underlying gastrointestinal risk.

MUCOSAL PROTECTION

Two methods are commonly employed to prevent the development of peptic ulceration and mucosal injury in patients taking NSAIDs: (i) co-therapy with a PPI, high-dose (2×) histamine-2-receptor antagonist (H_2RA), or the synthetic prostaglandin E1 analog, misoprostol; and (ii) substitution of a COX-2 inhibitor for a traditional NSAID. Although co-therapy with a standard-dose H_2RA may prevent duodenal ulcers (50–54), it has not been shown to prevent NSAID-related gastric ulceration. Enteric coating or buffering of NSAIDs and co-therapy with sucralfate have not been shown to be effective in preventing NSAID-related gastric or duodenal ulceration (55–59).

Misoprostol

Misoprostol was the first agent approved for the prevention of NSAID-related ulceration. Early studies in normal volunteers showed a marked reduction in the incidence of gastroduodenal ulcers in patients receiving NSAIDs in combination with misoprostol compared with those who received NSAIDs and placebo (60–62). Subsequent RCTs in patients suffering from osteoarthritis and rheumatoid arthritis revealed that misoprostol was significantly better than placebo, sucralfate, and ranitidine in the prevention of NSAID-related ulceration (63–69). An extensive meta-analysis of RCTs evaluating prevention strategies of NSAID-induced gastric ulceration showed that misoprostol was significantly more effective than H_2 receptor antagonists (70). A more recent meta-analysis revealed that co-therapy with misoprostol reduced the incidence of duodenal ulcers by 53% and gastric ulcers by 74%, when compared with placebo (71). Another RCT comparing a standard dose of misoprostol (200 mcg q.i.d.) with the PPI lansoprazole (in

doses of 15 and 30 mg daily) showed that 93% of patients taking misoprostol were protected from developing a gastric ulcer compared with 80 and 82% in the two lansoprazole groups, respectively over 12 weeks. This was not statistically significant (72). Patients who were ulcer free after 12 weeks of therapy were continued for another 12 weeks on the same regimen, and at the end of that time 43% of those on placebo, 83% on misoprostol, 83% on lansoprazole 30 mg, and 89% on lansoprazole 15 mg were still ulcer free (72).

In all of the above studies, the endoscopic visualization of an ulcer was utilized and interpreted as a surrogate end point for GI bleeding and other complications of gastric and duodenal ulcers. However, the end point that really matters in clinical practice and against which the clinically relevant therapeutic effect of any mucosal protective agent must ultimately be judged is the prevention of GI complications and upper GI bleeding in particular. A large, randomized, controlled outcome trial comparing misoprostol 200 mcg q.i.d. with placebo in 8,843 elderly patients (average age 83) with rheumatoid arthritis taking various NSAIDs showed a 40% reduction in serious upper GI complications among those taking the prostaglandin analog (23). In this, as well as other studies, the usefulness of misoprostol was limited by the occurrence of GI side effects, primarily cramping and diarrhea, and by compliance problems related to q.i.d. dosage. It should be noted, however, that there is evidence that lower doses (400–600 mcg/day) of misoprostol also confer a significant protective effect in the presence of a side effect profile similar to placebo (60–66).

Proton pump inhibitors

Proton pump inhibitors have been utilized extensively as co-therapy to prevent NSAID-induced peptic ulcers. Two large RCTs have been performed in osteoarthritis and rheumatoid arthritis patients with ulcers >3 mm in diameter or >10 erosions comparing omeprazole with placebo, misoprostol, and ranitidine in the prevention of gastric and duodenal ulcers (73–74). Patients were treated for 4–8 weeks with one of the active agents. Patients whose ulcers were considered healed were then randomized into a 6-month maintenance phase (73) where they were treated with omeprazole 20 or 40 mg daily or raniditine 150 mg b.i.d. in the first study and omeprazole 20 mg daily, misoprostol 200 mcg b.i.d. or placebo in the second study (74). Omeprazole co-therapy resulted in a significant reduction in the total number of NSAID-related ulcers when compared to ranitidine ($P = 0.004$). There was no placebo group in this study (73). Omeprazole was more effective than misoprostol in preventing duodenal ulcers and equally so in reducing gastric ulcers in the second study (74). Both drugs were significantly better than placebo ($P = 0.001$). It should be noted that what would be regarded as the lowest effective dose of misoprostol (400 mcg/day) was used as the comparator in this study and that most of the overall effect of omeprazole in preventing NSAID-related ulceration studies was due to a reduction in the incidence of duodenal ulcers. This may be due to the fact that the incidence of *H. pylori* infection was not determined prior to the inclusion of patients in these studies. Indeed, a *post hoc* analysis revealed that most of the added protection attributable to omeprazole use occurred among those with *H. pylori* infection. As previously noted, lansoprazole in a dose of 15 or 30 mg daily compared to misoprostol 800 mcg daily and placebo, was highly effective (80 and 82%, respectively) in preventing gastric ulcers in *H. pylori*-negative patients taking NSAIDs (72).

Two similar multicenter RCTs have recently been reported together. These compared esomeprazole 20 or 40 mg with placebo in the prevention of ulcers in patients taking NSAIDs or COX-2 inhibitors over a 6-month period. In the first study, which involved 844 patients recruited within the United States, ulcer rates were 20.4, 5.3, and 4.7% for placebo, esomeprazole 20 mg, and esomeprazole 40 mg, respectively. In the other study, which involved 585 patients from several countries, the respective ulcer rates were 12.3, 5.2, and 4.4%. Patients in both studies were *H. pylori*-negative and were considered at increased risk on the basis of age (above 60 years), or a history of documented gastric or duodenal ulceration within 5 years of entry into the study. None, however, had evidence of GI bleeding or perforation during the 6 months immediately preceding the study. Four hundred of the subjects out of the combined total of 1,429 were on COX-2 inhibitors and pooled data from the two studies for this subgroup revealed ulcer rates of 16.5% for placebo, 0.9% for esomeprazole 20 mg, and 4.1% for esomeprazole 40 mg. Overall, for patients taking COX-2 inhibitors or NSAIDs, ulcer rates were 17.0, 5.2, and 4.6% for the placebo, esomeprazole 20 and 40 mg groups, respectively (75). A recent case–control study matched 2,777 patients with endoscopically confirmed upper GI bleeding with 5,532 controls. In patients taking NSAIDs, PPI therapy was associated with a significant risk reduction for upper GI bleeding (relative risk 0.13 95% CI 0.09–0.19 vs. relative risk 0.30 95% CI 0.17–0.53) (76). Another recent endoscopic ulcer prevention study compared pantoprazole 20 and 40 mg daily with omeprazole 20 mg daily in 595 rheumatoid arthritis patients (>55 years of age) taking traditional NSAIDs daily. After 6 months, the probability of remaining in ulcer remission were 91 and 95% for pantoprazole 20 and 40 mg, respectively and 93% for omeprazole 20 mg (77). Thus, although misoprostol in full dosage (200 mcg q.i.d.) is very effective in the prevention of NSAID-related ulcer and its complications (72,74), GI side effects, primarily cramps and diarrhea, limit the use of this agent. Furthermore, the aforementioned more recent PPI studies have yielded results, which are at least as effective. Lower doses of misoprostol are not associated with these side effects but appear no more effective than standard dose PPI therapy (60,61,66). For all of these reasons PPIs have assumed dominance in NSAID-related upper GI injury prophylaxis and therapy. However, it needs to be pointed out that to date there have not been any randomized, prospective, controlled outcome trials that have evaluated the efficacy of PPIs in preventing the occurrence of complications resulting from NSAID-related ulcers. Nevertheless, co-therapy with omeprazole was documented to be effective in preventing

recurrent ulcer bleeding in a randomized trial of NSAID users with *H. pylori* infection who had prior ulcer bleeding (48). Data from observational studies and secondary analysis of a large-scale randomized trial also indicate that PPIs reduce the risk of NSAID-associated ulcer bleeding (61,78–79).

High-dose H_2RA

Systematic reviews have shown that double-dose (e.g., famotidine 40 mg two times daily) but not single-dose H_2RAs are effective in reducing the risk of NSAID-induced endoscopic gastric ulcers (50,80). Economic modeling suggests that co-therapy with an H_2RA may be a cost-effective strategy for prevention of ulcer bleeding in NSAID users. Brown *et al.* compared four strategies, namely, NSAIDs plus an H_2RA, NSAIDs plus a PPI, NSAIDs plus misoprostol, and COX-2 selective NSAIDs. They showed that the optimal strategy depends on the "willingness-to-pay," with NSAIDs plus an H_2RA being the least costly strategy (81). Another economic analysis of the above five strategies in patients with low- to average-gastrointestinal risk also suggested that there may be a case for prescribing H_2RAs in all patients requiring NSAIDs (82). Like PPIs, there have not been any randomized, clinical outcome trials that evaluate the efficacy of H_2RAs in chronic NSAID users.

COX-2 inhibitors

The search for a less gastrotoxic NSAID led to the development of the COX-2 inhibitors. It had been known for some time that NSAIDs inhibited the enzyme cyclooxygenase (COX), leading to a significant decrease in prostaglandin production. COX exists as two isoenzymes, COX-1 and COX-2. COX-1 is a constitutive enzyme and exists in many body tissues, including the stomach, where it facilitates the production of those prostaglandins considered to be important in gastric mucosal protection. COX-2, on the other hand, is an inducible enzyme and is associated with inflammation in the joints. It was postulated that the selective inhibition of COX-2 should lead to decreased inflammation in musculoskeletal tissues and, by sparing COX-1, to a decrease in the incidence of GI mucosal injury (83–88).

Early studies in normal volunteers seemed to bear out this hypothesis (89–91), which was further substantiated by an RCT of 742 patients over 50 years of age with arthritis. In the latter study, two doses of rofecoxib (25 or 50 mg) were compared with 2,400 mg of ibuprofen or placebo. After 24 weeks, ulcer rates were 9.6% for rofecoxib 25 mg, 14.7% for rofecoxib 50 mg, 45.8% for ibuprofen 2,400 mg, and 9.9% for placebo (12 weeks) (92). In another RCT involving 537 patients with osteoarthritis or rheumatoid arthritis, celecoxib 200 mg b.i.d. was compared with naproxen 500 mg b.i.d. After 12 weeks, the cumulative incidence of gastric and duodenal ulceration for celecoxib was 9% and for naproxen 41%. In the group which received celecoxib, the occurrence of ulcers was significantly associated with a number of factors: *H. pylori* positivity, concurrent aspirin usage, and a history of ulcers (93). In a similar study, 181 elderly subjects (65–75 years old) were randomized to receive naproxen 500 mg b.i.d., valdecoxib 40 mg b.i.d. (a supra-therapeutic dose), or placebo. Ulcer rates were 18, 0, and 3%, respectively (94). In a study designed to determine whether a COX-2 inhibitor alone was adequate for prevention of recurrent ulcer bleeding among a group of very high-risk patients (i.e., those with a recent GI bleed), 284 patients were randomized to receive either celecoxib 200 mg b.i.d. plus placebo or diclofenac 75 mg b.i.d. plus omeprazole 20 mg daily. Ulcer rates after 6 months were 19 and 26% for the celecoxib/placebo and the diclofenac/omeprazole groups, respectively. Rebleeding rates were 4.9 and 6.4%, respectively, over the same time period. There was no significant difference between ulcer recurrence and rebleeding rates for the two groups. It would appear that, in very high-risk patients, neither a COX-2 inhibitor administered on its own or the combination of a nonselective NSAID with a PPI will reduce the risk of ulcer recurrence or rebleeding (95) Recently, a double-blind randomized trial assessed the efficacy of combination of a PPI and a COX-2 inhibitor in patients with very high risk of GI complications. In all 441 consecutive patients with nonselective-NSAID-associated ulcer bleeding were enrolled. They were given celecoxib 200 mg two times daily after confirmation of ulcer healing and a negative test for *H. pylori* infection. Patients were randomly assigned to a PPI (esomeprazole 20 mg two times daily) or placebo. Low-dose aspirin was allowed during the study after the CV risks of COX-2 inhibitors became apparent. After a median follow-up of 13 months, 8.9% of the celecoxib-alone group had recurrent ulcer bleeding compared with none of the combined therapy group ($P=0.0004$) (96).

There have been three large randomized, controlled, outcome trials comparing COX-2 inhibitors to traditional NSAIDs (5,6,97). A study (CLASS) of 8,059 patients with arthritis compared celecoxib 400 mg b.i.d., with ibuprofen 800 mg t.i.d., or diclofenac 75 mg b.i.d. (5). A non-significant 50% reduction in ulcer complications was observed in the celecoxib group in comparison to those who received the conventional NSAID after 6 months of therapy. However, after 1 year, there was little or no difference between the three groups. This study allowed patients on low-dose aspirin to participate; 19% of subjects fell into this category. The exclusion of this latter group from the 6-month analysis resulted in ulcer complication rates of 0.5% for the celecoxib and 1.5% for the NSAID groups respectively, a significant difference ($P=0.04$). There were no differences at 6 months between any of the interventions among patients who had consumed low-dose aspirin (5). Another large trial (VIGOR) compared outcomes for 8,076 rheumatoid arthritis patients taking either 500 mg of naproxen b.i.d. or 50 mg of rofecoxib daily. In this study, low-dose aspirin users were excluded. At 6 months, rofecoxib was associated with a significantly lower incidence of GI events (2.1 vs. 4.5%, $P<0.001$), and GI complications (0.6 vs. 1.42%, $P=0.005$) (6). However, a subsequent trial in osteoarthritis patients, comparing ulcer rates in patients taking placebo, low-dose aspirin, low-dose aspirin plus rofecoxib 50 mg daily, and ibuprofen 2,400 mg daily revealed no difference between the aspirin/rofecoxib and the ibuprofen groups after 12 weeks, again demonstrating the elimination of

the beneficial effect of COX-2 inhibitors in the presence of low-dose aspirin (97). Lumiracoxib is a new COX-2 inhibitor, which has recently been evaluated in over 18,000 subjects, and is currently being considered for approval in the United States. In this study (TARGET), lumiracoxib was compared to traditional NSAIDs in patients with arthritis. After 1 year, a significant reduction in ulcer complication rates was noted for lumiracoxib among the entire study population (0.3 vs. 0.9%) as well as among those who were not consuming aspirin (0.2 vs. 0.9%) (98). Two large nested case–control studies by the same group of investigators showed a significantly better GI safety profile for coxibs than for traditional NSAIDs for both UGI bleeding and other complications. In both studies, the concomitant use of low-dose aspirin negated the beneficial effect of the COX-2 inhibitors (99–100). In a study of 2,587 patients with colorectal adenomas who were randomized to receive either rofecoxib 25 mg daily or placebo for 3 years, the incidence of confirmed complicated GI events (bleeding, perforation, and symptomatic ulcer) was significantly higher in the patients taking rofecoxib. (0.88 vs. 0.18 events per 100 patient years; relative risk, 4.9; 95% CI, 1.98–14.54) (101).

Etoricoxib is another COX-2 inhibitor currently in use in Europe. In a report summarizing the results from three prospective randomized, double-blind trials, 34,701 arthritic patients were treated with 60 or 90 mg of etoricoxib or 150 mg of diclofenac daily. This study included patients on low-dose aspirin and/or PPI therapy. It was found that the overall incidence of uncomplicated GI events was significantly less with etoricoxib than with diclofenac (Hazard ratio 0.69, 95% CI; 0.57–0.83) ($P < 0.001$). There were no differences between the groups for complicated events (bleeding, perforation, and obstruction). There were no significant differences in treatment effects between the groups in regard to those patients taking PPIs and/or low-dose aspirin (102).

In a Cochrane systematic review of the GI safety of COX-2 inhibitors, COX-2 inhibitors produced significantly fewer gastroduodenal ulcers (relative risk, 0.26; 95% confidence interval, 0.23–0.30) and ulcer complications (relative risk, 0.39; 95% confidence interval, 0.31–0.50), as well as fewer withdrawals caused by GI symptoms when compared to nonselective NSAIDs (103).

Cardiovascular risks associated with coxibs and NSAIDs

Reports of cardiovascular side effects in relation to the COX-2 inhibitors have limited their usefulness. On this basis, rofecoxib and valdecoxib have both been removed from the market by the manufacturers at the request of the FDA (104). Valdecoxib was also associated with toxic epidermal necrolysis. An increase in cardiovascular events in relation to COX-2 use was first noted in the VIGOR trial of rofecoxib in which patients taking low-dose aspirin were excluded; the incidence of cardiovascular events was statistically higher in patients taking rofecoxib compared to those receiving naproxen (0.5 vs. 0.1%) (6). The CLASS trial, which compared celecoxib with either diclofenac or ibuprofen, revealed no significant difference in the number of cardiovascular events between any of the agents in either aspirin users or non-users (5). The large lumiracoxib TARGET study demonstrated that the rates of myocardial infarction on lumiracoxib were numerically lower than on ibuprofen but higher than on naproxen (98). This study was, however, underpowered to detect a difference in CV outcomes between treatment groups (105). Further data regarding cardiovascular thromboembolic events associated with COX-2 inhibitors became available from two long-term studies of colon polyp prevention using rofecoxib (APPROVE) (106) and celecoxib (APC) (107). In the APPROVE trial, the incidence of stroke, myocardial infarction, or sudden cardiac death in patients taking rofecoxib 25 mg a day was two times that of patients taking placebo, resulting in the termination of the study. In the APC trial, the occurrence of the same cardiovascular events was significantly higher for celecoxib only at the very high dose of 400 mg b.i.d. (hazard ratio 1.9, 95% CI 1.0–3.3). The lower dose of celecoxib, 200 mg b.i.d., was associated with a significantly lower degree of risk (hazard ratio 1.5, 95% CI 0.8–2.8).

Emerging evidence suggests that both coxibs and NSAIDs, with the possible exception of full-dose naproxen, increase CV risk. In a meta-analysis of case–control and cohort studies, high-dose rofecoxib (>25 mg/day) was associated with an increase in CV events. Celecoxib did not increase CV events, though an increased risk could not be excluded with doses >200 mg/day. Both diclofenac and indomethacin were associated with an increased CV risk similar to that of rofecoxib (108). In a meta-analysis of published and unpublished randomized trials of COX-2 inhibitors, all COX-2 inhibitors were associated with an increased CV risk compared to placebo (rate ratio 1.42, 95% CI 1.13 to 1.78; $P = 0.003$). This was largely attributable to an increased risk of myocardial infarction with little difference in other vascular outcomes. A dose-dependent increase in CV events was also observed with celecoxib. There was no significant difference in CV risk between COX-2 inhibitors and nonselective NSAIDs. Naproxen was the only possible exception as it was not associated with an increase in CV events (109).

Conclusions

(i) Misoprostol, when given in full doses (800 mcg/day) is very effective in preventing ulcers, and ulcer complications in patients taking NSAIDs. Unfortunately, its usefulness is limited by its GI side effects. When given in lower doses its side-effect profile is the same as that of PPIs, and it is equally effective.

(ii) PPIs significantly reduce gastric and duodenal ulcers and their complications in patients taking NSAIDs or COX-2 inhibitors.

(iii) COX-2 inhibitors are associated with a significantly lower incidence of gastric and duodenal ulcers when compared to traditional NSAIDs. However, this beneficial effect is negated when the patient is taking concomitant low-dose aspirin. The usefulness of these agents has also been reduced by their association with myocardial infarction and other thrombotic CV events.

The lowest possible dose of celecoxib should, therefore, be used in order to minimize the risk of CV events.

(iv) Although superior to placebo, high-dose H_2RAs can reduce the risk of NSAID-induced endoscopic peptic ulcers. They are significantly less effective than PPIs, however, there is no clinical outcome data to prove that this strategy prevents ulcer complications.

STRATEGIES FOR THE PREVENTION OF NSAID-RELATED ULCER COMPLICATIONS

Several risk factors including patient age, co-morbidities, concurrent medications, prior medical history, and *H. pylori* infection, have been demonstrated in a variety of studies, with a considerable degree of consistency, to increase the risk of NSAID-related GI injury. The identification of these risk factors together with the advent of multiple protective strategies has led to the concept of therapy tailored according to risk (110). An approach to risk stratification is illustrated in **Table 1**. Gastrointestinal risk is arbitrarily stratified into low (i.e., no risk factors), moderate (presence of one or two risk factors), and high-risk group (multiple risk factors, a history of ulcer complications, or concomitant use of corticosteroids or anticoagulants). The consensus opinion of most experts in the field is that patients with a history of a recent complicated peptic ulcer are at very high risk and should be treated with NSAIDs with extreme caution and in the presence of maximal protective measures. Among such patients it is best to avoid NSAID treatment entirely; however, if anti-inflammatory treatment must be used, a COX-2 inhibitor plus misoprostol or a PPI therapy (95–96) should be employed. Patients with a history of peptic ulcer disease, with or without complications, at any time in the past, and concurrent use of aspirin (including low dose), antiplatelet drugs (e.g., clopidrogel), anticoagulants (e.g., warfarin), or corticosteroids, or two or more risk factors are also placed in a high-risk category; these patients should also be treated with a COX-2 inhibitor and either misoprostol or PPI therapy (5,6,23,72–75). Patients considered to be at moderate risk (**Table 1**) can be treated with a COX-2 inhibitor alone or an NSAID plus misoprostol or a PPI (89–94). Patients without risk factors are at low risk for NSAID-related peptic ulcer complications and no protective measures are required (111).

Table 1. Patients at increased risk for NSAID GI toxicity

High risk
1. History of a previously complicated ulcer, especially recent
2. Multiple (>2) risk factors
Moderate risk (1–2 risk factors)
1. Age >65 years
2. High dose NSAID therapy
3. A previous history of uncomplicated ulcer
4. Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants
Low risk
1. No risk factors

H. pylori is an independent and additive risk factor and needs to be addressed separately (see text and recommendations).

Current evidence indicates that *H. pylori* infection increases the risk of peptic ulcer in patients taking NSAIDs (38–42) and that eradication of *H. pylori* reduces their ulcer risk (43–49). Furthermore, economic modeling strongly suggests that eradication of *H. pylori* is cost-effective in primary prevention of peptic ulcers in average-risk NSAID users. Thus, there is a potential advantage of testing for *H. pylori* infection and eradicating the infection if positive in all patients requiring NSAID therapy. Whether co-therapy with a gastroprotective agent is needed after eradication of *H. pylori* depends on individual patients' underlying gastrointestinal risk.

Patients with risk factors for cardiovascular disease (i.e., prior history of a cardiovascular event, diabetes, hypertension, hyperlipidemia, and obesity) often receive prophylactic aspirin. They may benefit from the substitution of a less cardiotoxic NSAID instead of a COX-2 inhibitor. Naproxen may be the agent of choice as it may have some cardioprotective properties (76,98,108,109,112). In addition, these patients should receive a PPI or misoprostol because the combination of naproxen and low-dose aspirin markedly increases the risk of GI bleeding. Patients at very high GI risk who also have increased CV risk should not be treated with NSAIDs or coxibs and another form of treatment should be considered. These recommendations are summarized in **Table 2**.

Table 2. Summary of recommendations for prevention of NSAID-related ulcer complications

	Gastrointestinal risk[a]		
	Low	**Moderate**	**High**
Low CV risk	NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	NSAID+PPI/misoprostol	Alternative therapy if possible or COX-2 inhibitor+PPI/misoprostol
High CV risk[b] (low-dose aspirin required)	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy

[a]Gastrointestinal risk is stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications, or concomitant use of corticosteroids or anticoagulants). [b]High CV risk is arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for *H. pylori*, and if the infection is present, eradication therapy should be given.

Recommendations

(i) Patients requiring NSAID therapy who are at high risk (e.g., prior ulcer bleeding or multiple GI risk factors) should receive alternative therapy, or if anti-inflammatory treatment is absolutely necessary, a COX-2 inhibitor, and co-therapy with misoprostol or high-dose PPI.
Level of evidence 1 . Strength of recommendation B .

(ii) Patients at moderate risk can be treated with a COX-2 inhibitor alone or with a traditional nonselective NSAID plus misoprostol or a PPI.
Level of evidence 1 . Strength of recommendation B .

(iii) Patients at low risk, i.e., no risk factors, can be treated with a non-selective NSAID.
Level of evidence 1 . Strength of recommendation A .

(iv) Patients for whom anti-inflammatory analgesics are recommended who also require low-dose aspirin therapy for cardiovascular disease can be treated with naproxen plus misoprostol or a PPI.
Level of evidence 2 . Strength of recommendation C .

(v) Patients at moderate GI risk who also are at high CV risk should be treated with naproxen plus misoprostol or a PPI. Patients at high GI and high CV risk should avoid using NSAIDs or coxibs. Alternative therapy should be prescribed.
Level of evidence 2 . Strength of recommendation C .

(vi) All patients regardless of risk status who are about to start long-term traditional NSAID therapy should be considered for testing for *H. pylori* and treated, if positive.
Level of evidence 2 . Strength of recommendation A .

Ratings for level of evidence and strength of recommendations are based on the criteria noted before derived from recommendations from the GRADE working group (113).

Level of evidence

(1) Level of evidence strongly in favor of recommendation.
(2) Level of evidence favors recommendation.
(3) Level of evidence in favor of recommendation is equivocal.
(4) Level of evidence does not favor recommendation.

Strength of recommendations

(A) Strong evidence for multiple published, well-controlled randomized trials or a well-designed systemic meta-analysis.
(B) Strong evidence from at least one quality-published randomized controlled trial or evidence from published, well-designed, cohort or matched case–control studies.
(C) Consensus of authoritative expert opinions based on clinical evidence or from well designed, but uncontrolled or non-randomized clinical trials.

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