A Clinician's Guide to the Selection of NSAID Therapy

The authors of this article present a 4-quadrant matrix based on 2 key clinical parameters: risk for adverse gastrointestinal (GI) events related to nonsteroidal anti-inflammatory drug (NSAID) use, and aspirin use based on cardiovascular risk.

The matrix was developed to help clinicians assess risk in their patients and choose appropriate treatment strategies that emphasize therapeutic benefit, minimize the risk of NSAID-related GI events, and address the pharmacoeconomics of available treatment options.

The 2 quadrants on the left side of the matrix represent patients at no risk or low risk for NSAID-related adverse GI events, and the 2 quadrants on the right represent patients at moderate or high risk for NSAID-related GI events. Similarly, the 2 upper quadrants represent patients who do not use or require aspirin for cardiovascular protection, and the 2 lower quadrants represent patients who do require aspirin for this purpose.

Thus, the 2 x 2 matrix delineates 4 categories of risk: no aspirin/ no or low GI risk; no aspirin/ GI risk; aspirin/ no or low GI risk; and aspirin/ GI risk (Figure).

Patients in the no aspirin/ no or low GI risk category should be treated with a traditional NSAID. If GI symptoms develop, an antacid or an antisecretory agent can be added. Although cyclooxygenase-2 (COX-2) selective inhibitors, or coxibs, may be used in these patients, cost-effectiveness analyses suggest that the higher cost of these drugs yield relatively poor values in the low-risk group.

Patients in the no aspirin/ GI risk category should be treated with a COX-2 inhibitor in combination with an antisecretory agent, such as a proton pump inhibitor (PPI) or H2-receptor antagonist, if GI symptoms develop. For patients in this category who are already taking a PPI for another indication, a traditional NSAID should be used.

Patients in the aspirin/ no or low GI risk category should be treated with a traditional NSAID plus a PPI or a gastroprotective agent such as misoprostol. An alternative approach is to use a COX-2 selective inhibitor plus a PPI or a gastroprotective agent.

Patients in the aspirin/ GI risk category should be treated with a PPI or gastroprotective agent regardless of the type of NSAID—traditional or COX-2 inhibitor—used.

The authors emphasize the importance of including not only the patient’s risk for adverse GI events, but also the patient’s need for aspirin prophylaxis in the risk assessment. Using the matrix simplifies both the risk assessment and the choice of appropriate therapy.


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**Figure. Risk Stratification Matrix**

<table>
<thead>
<tr>
<th>No Aspirin</th>
<th>Traditional NSAID</th>
<th>COX-2 inhibitor OR If on PPI, add traditional NSAID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin*</td>
<td>Traditional NSAID plus gastroprotective agent</td>
<td>Gastroprotective agent irrespective of NSAID used</td>
</tr>
</tbody>
</table>

* Need for aspirin is based on patient's cardiovascular risk.

NSAID = nonsteroidal anti-inflammatory drug; GI = gastrointestinal.
**Ulcer Prevention in Long-Term Users of Nonsteroidal Anti-Inflammatory Drugs: Results of a Double-Blind, Randomized, Multicenter, Active- and Placebo-Controlled Study of Misoprostol vs Lansoprazole**

In this study comparing 12 weeks of therapy with lansoprazole 15 mg, lansoprazole 30 mg, misoprostol 800 µg, and placebo, both doses of lansoprazole were found to be superior to placebo for the prevention of gastric ulcers due to nonsteroidal anti-inflammatory drugs (NSAIDs) but not superior to misoprostol. However, when the poor compliance and adverse effects of misoprostol were considered, lansoprazole and full-dose misoprostol were deemed to be clinically equivalent.

Because results from studies that report prevention of ulcer recurrence among long-term users of NSAIDs who have not been stratified by Helicobacter pylori status do not necessarily apply to the large number of NSAID users who do not have H pylori infection, this 12-week, prospective, double-blind, multicenter study specifically enrolled long-term NSAID users with a history of endoscopically documented gastric ulcer who were negative for H pylori infection. Ulcer status was determined by endoscopy at 4 weeks, 8 weeks, and 12 weeks.

Of the 537 patients enrolled in the study, 136 were randomized to lansoprazole 15 mg daily, 133 to lansoprazole 30 mg daily, 134 to misoprostol 200 µg, 4 times daily, and 134 to placebo. One patient in the placebo group and 1 patient randomized to lansoprazole 30 mg did not take the study medication and were excluded from the intent-to-treat analysis. An additional 82 patients were excluded from the per-protocol analysis because of nonadherence (fewer than 14 days of therapy and/or taking less than 67% of the prescribed study medication; n = 33, including 19 in the misoprostol group), inappropriate ulcer history (n = 6), positive for H pylori infection at baseline (n = 15), and other reasons (n = 10).

Evaluable patients in both lansoprazole groups remained free from gastric ulcer significantly longer than those in the placebo group (P < .001), with no difference between the lansoprazole dosage groups. Similarly, evaluable patients in the misoprostol group remained free from gastric ulcer significantly longer than those in the placebo group (P < .001), the lansoprazole 15 mg group (P = .01), and the lansoprazole 30 mg group (P = .04).

Absence of a gastric ulcer after 8 or 12 weeks of treatment also differed by treatment group. By week 12, 51% of placebo patients were free from ulcer, compared with 93% in the misoprostol group, 80% in the lansoprazole 15 mg group, and 82% in the lansoprazole 30 mg group.

A significantly higher proportion of patients in the misoprostol group reported treatment-related adverse events and early withdrawal from the study. When the impact of study withdrawal on ulcer development was considered (as treatment failures), the proportion of patients considered treatment successes was 69% for each of the 3 treatment groups vs 35% for placebo.

An analysis of patient diaries kept during the study revealed that patients in both lansoprazole groups experienced significantly less severe and significantly fewer days with daytime abdominal pain than evaluable patients in the misoprostol group. Those receiving lansoprazole 15 mg daily also had significantly less severe (P = .01) and significantly fewer days (P = .001) with nighttime abdominal pain than those receiving misoprostol. The authors of this report note the theoretical and practical advantages of lansoprazole compared with misoprostol, including once daily dosing and fewer adverse events.


**Controversies in COX-2 Selective Inhibition**

In this report, which was prepared by 24 experts in rheumatology, gastroenterology, nephrology, and cardiology under the auspices of the International COX-2 Study Group, the authors review several controversies in cyclooxygenase-2 (COX-2) inhibitor therapy, summarize the current data regarding each controversy, and provide data-based recommendations.

Three of the controversies center on the safety and evaluation of the COX-2 inhibitors in the upper gas-
trointestinal (GI) tract, whereas 3 center on the renal, cardiorenal, and cardiovascular effects of these agents.

Regarding the GI safety of COX-2 selective inhibitors compared with traditional nonsteroidal anti-inflammatory drugs (NSAIDs), the panel cites current data indicating that the COX-2 inhibitors are safer than traditional NSAIDs, with a lower incidence of clinically important upper GI events.

Regarding the need for gastroprotection with COX-2 therapy, the panel notes that patients treated with these agents generally do not need additional therapy for upper GI ulcer prophylaxis. They do note, however, that GI symptoms not related to upper GI ulcers (eg, dyspepsia) may develop.

With regard to the use of concomitant aspirin therapy for cardiovascular prophylaxis in patients treated with COX-2 inhibitors, the panel notes that all patients taking low-dose aspirin for cardioprotection and who are at risk for upper GI ulcer complications should receive therapy with an agent that protects the GI mucosa. This holds true regardless of whether the patient is taking a traditional NSAID or a COX-2 inhibitor.

Because the COX-2 inhibitors and traditional NSAIDs have similar effects on renal function, the panel recommends that all NSAIDs be used with caution in patients with potential renal failure (ie, those with preexisting cardiac, renal, or hepatic disease), and that patients be observed carefully.

Because the effects of traditional NSAIDs and COX-2 selective inhibitors on blood pressure and edema appear to be similar, the panel recommends that these conditions be carefully monitored in all patients receiving therapy with these agents.

Regarding therapy with low-dose aspirin in conjunction with a COX-2 inhibitor in patients with arthritis who are at risk for cardiovascular disease, the panel recommends that aspirin prophylaxis be continued or initiated along with a traditional NSAID or a COX-2 inhibitor.

Despite their recent introduction into clinical practice, there is an unprecedented amount of data on the COX-2 selective inhibitors. Nevertheless, the panel points out that there are still a number of unanswered questions regarding these agents, including the following:

- Do COX-2 inhibitors delay healing of mucosal damage relative to traditional NSAIDs?
- What are the underlying causes of adverse events associated with COX-2 selective inhibitors?
- Aside from patients at risk for NSAID-induced upper GI ulcers and complications, should any other patient groups be candidates for therapy with COX-2 inhibitors?
- What are the potential clinical benefits of COX-2 inhibitors compared with other anti-inflammatory agents or acetaminophen?
- What are the potential benefits and risks of COX-2 inhibitors on bone resorption and bone formation?
- Would direct comparisons between celecoxib and rofecoxib in selected patient populations in randomized controlled trials help define their preferential use compared with traditional NSAIDs?
- Would randomized controlled trials reveal clinically significant differences between celecoxib and rofecoxib?

The report concludes with a call for continued investigation and additional well-designed randomized controlled trials to answer these questions.


**Celecoxib Versus Diclofenac and Omeprazole in Reducing the Risk of Recurrent Ulcer Bleeding in Patients with Arthritis**

In this 6-month study involving 287 patients with arthritis who presented with recent ulcer bleeding, treatment with the cyclooxygenase-2 (COX-2) selective inhibitor celecoxib was found to be as effective as treatment with the traditional nonsteroidal anti-inflammatory drug (NSAID) diclofenac plus the proton pump inhibitor (PPI) omeprazole in preventing recurrent bleeding.

As described by the study investigators, patients were randomly assigned to celecoxib 200 mg twice daily (twice the maximal dose for osteoarthritis) plus daily placebo (n = 144) or diclofenac 75 mg twice
daily plus omeprazole 20 mg daily (n = 143) for 6 months after ulcers had healed and cultures for Helicobacter pylori were negative. Use of antacids, acetaminophen, non-N SAID analgesics, disease-modifying antirheumatic drugs, and low-dose aspirin (up to 325 mg daily) were permitted during the study, but N SAIDs other than diclofenac, misoprostol, histamine H₂-receptor antagonists, sucralfate, and PPIs other than omeprazole were prohibited.

Patients in both groups were similar for baseline characteristics, such as age, sex distribution, current smoking and alcohol status, size and location of bleeding ulcers, number of bleeding episodes, presence and number of coexisting medical conditions, type of arthritis, and previous H pylori infection. More patients in the celecoxib group required transfusions and had serum creatinine levels >1.2 mg/dL, whereas more patients in the diclofenac plus omeprazole group used low-dose aspirin concomitantly.

In the intention-to-treat analysis, recurrent bleeding occurred in 7 patients randomized to celecoxib and in 9 patients randomized to diclofenac plus omeprazole. The probability of recurrent bleeding during the 6-month treatment period was 4.9% for patients taking celecoxib and 6.4% for patients taking diclofenac plus omeprazole.

Of the 260 patients who did not take concomitant low-dose aspirin, 6 taking celecoxib and 7 taking diclofenac plus omeprazole had recurrent ulcer bleeding, for a probability of recurrent bleeding during the study of 4.5% and 5.6%, respectively. Patients' global assessment of disease activity and arthritis pain were similar between the groups, as were discontinuation rates because of adverse events (10.5% in the celecoxib group vs 9.8% in the diclofenac plus omeprazole group) and lack of efficacy (1.4% in both groups). Renal adverse events, including hypertension, peripheral edema, and renal failure, were common, especially in patients with renal impairment at baseline (51.4% in patients taking celecoxib and 40.7% in those taking diclofenac plus omeprazole).

Most of the patients enrolled in the study had one or more risk factors for adverse gastrointestinal events in addition to a recent history of ulcer bleeding. These risk factors include advancing age (mean age, 66.5 years in the celecoxib group; 68.8 years in the diclofenac plus omeprazole group) and coexisting medical conditions.

Neither regimen can completely eliminate the risk of recurrent ulcer complications in high-risk patients. The investigators suggest that subsequent studies be performed to evaluate whether a COX-2 inhibitor plus a PPI or misoprostol will eliminate the risk of ulcer complications in at-risk patients.


Lansoprazole for the Prevention of Recurrences of Ulcer Complications from Long-Term Low-Dose Aspirin Use

As the results of this year-long, placebo-controlled study demonstrate, therapy with the proton pump inhibitor lansoprazole in addition to eradication of Helicobacter pylori infection significantly reduces the rate of recurrent ulcer complications in patients taking low-dose (100 mg) aspirin daily to prevent cardiovascular or cerebrovascular disease.

The study involved 123 patients between 18 and 80 years of age who had developed ulcer complications after taking low-dose (100 mg daily) aspirin continuously for at least 1 month and were also positive for H pylori infection. After ulcer healing and eradication of infection were confirmed by endoscopy, the patients were randomly assigned to treatment with lansoprazole 30 mg daily (n = 62) or placebo (n = 61) plus 100 mg aspirin daily for 12 months.

Ulcer healing and eradication of infection were accomplished by twice-daily treatment with lansoprazole 30 mg, amoxicillin 1 g, and clarithromycin 500 mg for 1 week. Patients with endoscopic evidence of unhealed ulcers after 1 week of therapy were given famotidine 20 mg twice daily for another 8 weeks, while those with residual H pylori infection, as indicated by positive rapid urease test results or histologic examination, received a 1-week course of twice-daily ranitidine bismuth citrate 400 mg, amoxicillin 1 g, and metronidazole 400 mg. Patients with unhealed ulcers and 2 unsuccessful attempts at eradication of H pylori were withdrawn from the study.
Patients were observed on an outpatient basis, with office visits every 2 months. During this time, they were allowed to take an antacid to relieve mild symptoms of dyspepsia, and told to visit the outpatient clinic if they had persistent ulcer symptoms that were not relieved by the antacid. They were also told to go to the emergency department if they had melena, hematemesis, or sudden onset of severe epigastric pain.

After a median follow-up of 12 months (range, 3 to 12 months), 9 of 61 patients in the placebo group had recurrent ulcer complications compared with only 1 of 62 patients in the lansoprazole group, \( P = .008 \).

Of the 10 patients who developed recurrent ulcer complications during the study, 4 (all in the placebo group) had evidence of recurrent \( H \) pylori infection and 2 had taken nonsteroidal anti-inflammatory drugs (NSAIDs) within 4 weeks before the onset of complications. Self-reports revealed that 4 patients in the lansoprazole group and 6 patients in the placebo group did not comply with therapy. In the lansoprazole group, 1 patient discontinued therapy because of intolerance to the drug, 1 discontinued aspirin use, and 2 were lost to follow-up. In the placebo group, 2 patients discontinued aspirin use, 2 were lost to follow-up, and 2 used NSAIDs.

The study investigators note that the addition of lansoprazole significantly reduced the rate of recurrence of ulcer complications, confirming findings of an epidemiologic study demonstrating a reduced risk of ulcer bleeding in patients taking low-dose aspirin and a proton pump inhibitor concurrently.


**Nonsteroidal Anti-inflammatory Drugs: Overall Risks and Management. Complementary Roles for COX-2 Inhibitors and Proton Pump Inhibitors**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are well recognized as causes of peptic ulcers and ulcer complications. However, the extent to which NSAIDs affect gastrointestinal (GI) disease and non-GI disease, their interaction with other risk factors, and approaches to optimizing management of the subgroups of patients taking NSAIDs remain poorly understood.

Accordingly, the authors suggest treatment strategies for various patient subgroups that consider non-specific GI risks, minimization of residual risk, and the importance of non-GI toxicity. In presenting these strategies and their underlying rationales, the authors describe the complementary roles of cyclooxygenase-2 (COX-2) selective inhibitors and proton pump inhibitors (PPIs).

Estimates of the amount of GI disease attributable to NSAID use vary widely, possibly because epidemiologic studies do not distinguish between causal and noncausal associations or because estimates based on events seen in high-risk populations are assumed to apply generally. Nevertheless, it has been estimated that between 20% and 25% of the more than 8500 hospitalizations for gastric and duodenal ulcer bleeding per year in the United Kingdom are due to nonaspirin NSAID use, with aspirin use accounting for an additional 10%. Estimates from epidemiologic studies in the United States are even higher, although the reasons are unclear.

Estimates from clinical trials in both the United Kingdom and the United States yield similar estimates of risk. However, in 3 large cohort studies that estimated the total risk of hospitalization for GI complications associated with NSAID use to be between 1.3 and 2.2 events per 1000 patient-years, not all of these events were caused by NSAIDs.

The authors note that the amount of non-GI disease attributable to NSAID use—consequences of salt and water retention, renal failure, provocation of bronchospasm, hypersensitivity reactions—must also be considered when selecting analgesic and anti-inflammatory therapy for various patient subgroups, as should the effect of aspirin and nonaspirin NSAIDs on the thrombotic complications of vascular disease and the interactions between aspirin and nonaspirin NSAIDs.

Protective strategies include either concomitant prescription of a gastroprotective agent, such as misoprostol or a PPI, or substituting an NSAID with high GI toxicity with one with reduced GI toxicity. With regard to the latter strategy, the COX-2 selective inhibitors have been shown to offer substantial GI safety. However, these agents have also been shown to cause sodium and water retention, hypertension, and edema. In one study, rofecoxib 50 mg daily was
associated with a significantly higher rate of cardiovascular events than naproxen 1 g daily [Bombardier et al. N Engl J Med. 2000;343:1520-1528]. In another study, in which 21% of patients were permitted to take aspirin (up to 325 mg daily), celecoxib was no more effective than a traditional NSAID comparator in reducing peptic ulcer rates [Silverstein et al. JAMA. 2000;284:1247-1255].

As noted in the recommendations of the National Institute for Clinical Excellence (United Kingdom), there are 5 circumstances under which COX-2 inhibitors should be used: prolonged use of standard NSAIDs at maximum recommended doses; in patients 65 years of age or older; in patients with previous ulcer complications; in patients taking drugs that increase the risk of upper GI events (eg, anticoagulants or corticosteroids); and in patients with serious comorbidity.

Similarly, there are other consensus recommendations regarding restrictions on the use of COX-2 inhibitors and PPIs based on their higher cost. However, a decrease in the price of PPIs would make the combination of a traditional NSAID plus a PPI cheaper than a COX-2 inhibitor, and would also make the combination of a PPI and a COX-2 inhibitor a cost-effective strategy for very-high-risk patients who are generally at risk for GI events, even when they are not taking NSAIDs.

The authors emphasize that an overall reduction in NSAID toxicity is likely only if different treatment strategies are applied to different patient subgroups because not all patients face the same risk for adverse GI events. In addition, because most of the accessory risk factors that increase risk in NSAID users also increase risk in nonusers, any satisfactory protective strategy to reduce risk should consider overall risks in NSAID users and nonusers alike, as well as the reasons why some patients are at particular risk whereas others are not.

Based on consensus statements and recommendations, the authors suggest the following for different patient subgroups:

- For patients without ancillary risk factors, reducing the NSAID dose reduces risk.
- For patients with a past ulcer history, switching to a COX-2 inhibitor substantially reduces risk and makes the use of these agents practical and economically attractive.
- For older patients, switching from a standard NSAID to a COX-2 inhibitor reduces risk, but also leaves substantial residual risk, thus arguing for a traditional NSAID plus a PPI as an alternative strategy.
- For patients requiring high doses of NSAIDs, switching to a full-dose COX-2 inhibitor provides equivalent anti-inflammatory and analgesic effects without significantly increasing GI risk, although there may be an increase in risk for fluid retention.
- For patients requiring corticosteroids, switching to a COX-2 inhibitor would be beneficial if the corticosteroid is acting only as an NSAID-specific risk magnifier.
- For patients with Helicobacter pylori infection, eradication of infection is recommended because even in patients using COX-2 inhibitors, H pylori remains a source of continuing ulcer risk.
- For patients with cardiovascular disease, allowances must be made for concurrent aspirin and anticoagulant use, and use of a PPI with either a standard NSAID or a COX-2 inhibitor is recommended.
- For patients with coagulation defects or on anticoagulant therapy, use of COX-2 inhibitors is recommended, although monitoring prothrombin time is also desirable.