Strategies to Reduce the GI Risks of Antiplatelet Therapy

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Low-dose aspirin and other antiplatelet agents are widely used for the management of cardiovascular disease. Due to their action on cyclooxygenase, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with upper gastrointestinal (GI) side effects, including ulcers and bleeding. Although the risk with low-dose aspirin alone is less than that with NSAIDs, given its widespread use, aspirin-related toxicity has become a substantial health care issue. Factors associated with an increased risk of aspirin-related upper GI complications are still being elucidated but most importantly include a prior history of ulcer or GI bleeding, aspirin dose, and concomitant use with an NSAID, anticoagulant, or additional antiplatelet drug. Various strategies are available to minimize the risk of developing upper GI side effects in patients taking aspirin. Gastroprotective agents that seem effective are prostaglandin analogues and proton pump inhibitors. Eradication of Helicobacter pylori *also seems to reduce the risk of ulcers. Substitution by other antiplatelet agents such as clopidogrel alone does not seem to provide a safer alternative to low-dose aspirin for patients at high risk for GI side effects.*

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Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits cyclooxygenase (COX), a key enzyme in the biosynthesis of prostaglandins, making it an effective pain reliever at traditional dosages. At low doses (325 mg or less) it predominantly inhibits the COX-1 isoform, thereby affecting the synthesis of platelet thromboxane A_2. By interfering with platelet aggregation, these doses benefit patients with a history of or

at risk for cardiovascular (CV) disease. Because high doses of aspirin have considerable toxicity despite potent analgesic properties, low-dose aspirin (75-325 mg/day) is widely used for the primary and secondary prevention of CV disease.

Despite the therapeutic benefits, aspirin and other NSAIDs are associated with considerable upper gastrointestinal (UGI) toxicity, as they increase the risk for gastrointestinal (GI) side effects, ranging from dyspepsia to complicated ulcers. Although low-dose aspirin seems to have fewer UGI side effects than high-dose aspirin and other NSAIDs, the risk is still substantial.[1] Widespread use makes aspirin/NSAID-related GI complications the most common serious drug-related toxicity. With the recent withdrawal of rofecoxib and valdecoxib from the market and concerns about prothrombotic risks for other agents, there has been increased attention on strategies to reduce the overall risks of therapy for users of cyclooxygenase inhibitors.

Table 1
Management Strategies for Reducing the Risk of Antiplatelet Therapy

Strategy	Clinical Disadvantage
Discontinue aspirin	Loss of efficacy—thrombotic events
Use the lowest effective aspirin dose (< 80 mg)	Potential loss of efficacy for patients with aspirin resistance
Use a "safer" but "equally effective" antiplatelet drug	No data to support this approach; clopidogrel less safe than aspirin + PPI in high-risk patients
Eradicate *H. pylori*	Lack of familiarity with tests and treatment among non-gastroenterologists
Misoprostol	Associated with side effects (high incidence of diarrhea)
H_2-receptor antagonist	? effective at traditional doses
Proton-pump inhibitor	High cost

The Importance of Risk Factors

Numerous clinical strategies have been suggested to reduce the risk for GI events related to COX inhibitors (Table 1). Because only 1% to 2% of chronic aspirin users develop a symptomatic ulcer, and risk varies considerably across individuals, it is essential to assess individual patient risk for complications (Table 2). Symptoms, or the lack thereof, are not good predictors of NSAID complication risk. Half or more of patients admitted for treatment of a complication have no antecedent dyspeptic symptoms—perhaps due to the analgesic properties of the medication. A critically important and frequently underrecognized risk factor for GI complications is the use of multiple COX inhibitors. Specifically, the addition of low-dose aspirin to any NSAID (including COX-2 inhibitors) increases the risk of GI complications substantially.

Restricting Aspirin Use to Patients Who Benefit from It

The efficacy of low-dose aspirin for secondary prevention of CV disease is well documented. In a meta-analysis of 5 primary prevention trials, aspirin reduced the risk of nonfatal myocardial infarction (MI) and fatal coronary heart disease, but also increased the risk of hemorrhagic stroke and bleeding overall.[2] More recently, the Women's Health Study demonstrated that low-dose aspirin lowered the risk of ischemic stroke, but had no effect on the risk of MI or death due to CV disease, resulting in no significant difference being found between aspirin and placebo for the primary endpoint, a major CV event.[2] The risk of adverse events, such as hemorrhagic stroke and GI bleeding, is clearly outweighed by the benefits for patients with established CV disease. The decision to use aspirin for primary prevention of CV events should be made after considering an individual patient's CV risk and the probability of adverse events. The American Heart Association recommends that aspirin be considered for all apparently healthy men and women whose 10-year risk of a CV event is 10% or greater.[2]

The US Preventive Services Task Force recommends that a risk-benefit

Table 2
Risk Factors for Aspirin and NSAID-Associated Ulcer Complications (in order of relative importance)

1. Personal history of complicated ulcer disease
2. Concurrent use of more than one cyclooxygenase inhibitor
3. Use of high doses
4. Concurrent use of an anticoagulant
5. Personal history of uncomplicated peptic ulcer disease
6. Age > 70 years
7. Concurrent use of steroids

calculation be performed before recommending low-dose aspirin for primary prevention of CV events.[2] The Task Force concluded that the balance of risk and benefit of aspirin use was strongly tied to cardiac risk, and explicitly recommends prophylactic aspirin only for those with a 3% or greater 5-year risk of CV events. Calculation of such risk is easily performed using personal digital assistant- or Internet-based tools. Given this narrow therapeutic window, it is clear that a clinician's input is warranted before a patient begins taking aspirin for primary CV prophylaxis. However, many patients initiate aspirin therapy without consulting a health care provider, due to the media attention aspirin has received in such areas as chemoprevention of cancer and prophylaxis of Alzheimer's disease.

The GI risks of aspirin are reviewed in detail in this supplement by Dr. David A. Johnson. It is important to reemphasize that the 2-fold greater risk of GI bleeding for those taking chronic low-dose aspirin compared with those not taking aspirin is not reduced by enteric coating or by the use of buffering, as the toxicity is due to the systemic absorption of aspirin; thus, even transcutaneous aspirin may cause a bleeding ulcer.

Pathophysiology of NSAID Injury to the GI Tract

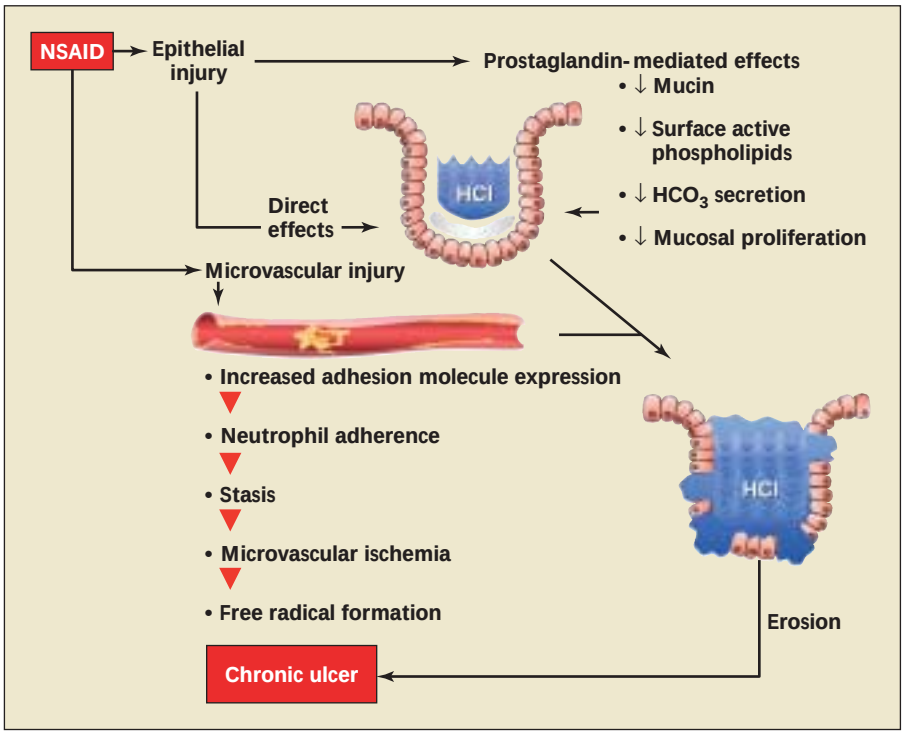
A complete discussion of the pathogenesis of NSAID-associated injury is beyond the scope of this article. Briefly, NSAIDs injure the gut mucosa in a 2-pronged attack: causing topical injury to GI mucosa and systemic effects induced by prostaglandin depletion. As prostaglandins are essential to the maintenance of intact GI defenses, in addition to normal platelet function, NSAIDs such as aspirin both promote ulcer formation and enhance bleeding.[3]

Prostaglandin depletion leads to a quantitative and qualitative reduction of mucous barrier function, inhibition of bicarbonate secretion, decreased mucosal proliferation, and increased acid secretion. Some or all of these changes may increase the risk of peptic ulcer formation and serious GI complications (Figure 1). Two isoforms of COX, COX-1 and COX-2, have contrasting roles: whereas COX-1 is needed for maintaining normal GI and platelet function, COX-2 is induced in areas of inflammation.

Because inhibition of COX-2 is the target of anti-inflammatory drug therapy, agents that selectively block COX-2 while having little to no effect on COX-1 have been considered effective agents for treating arthritis and pain, with reduced GI toxicity. This "COX-2 hypothesis" has been challenged by animal studies indicating that *both* COX-1 and COX-2 must be inhibited for gastric ulceration to occur. Interestingly, the selective inhibition of neither COX-1 alone nor COX-2 alone caused gastric damage, whereas inhibition of both COX isoforms produced gastric ulceration.[4] Thus, the explanation for the reduced GI toxicity of COX-2–specific inhibitors may be their lack of dual COX inhibition rather than their COX-1–sparing effects. In this framework, taking both cardioprotective aspirin (primarily a COX-1 inhibitor at low doses) and a COX-2 inhibitor creates the same ulcer risk as a traditional NSAID.

A high percentage of individuals requiring cardioprotective doses of aspirin have chronic pain and receive a traditional NSAID or coxib. A survey that queried chronic coxib users found that 50% or more were taking aspirin.[5] Whereas it is relatively

Figure 1. *Mechanisms of nonsteroidal anti-inflammatory drug (NSAID) injury to the upper gastrointestinal tract. Acid plays an important secondary role in perpetuating the damage, explaining why potent acid suppression is effective in prevention of ulcer development. Reprinted with permission from Scheiman.[3]*



well-documented that the use of multiple traditional NSAIDs increases the risk for GI complications, the use of aspirin in combination with either a traditional NSAID or a coxib is less well recognized as a GI risk factor by clinicians. Moreover, because coxibs were heralded as having an improved safety profile, owing to fewer toxic GI effects than traditional NSAIDs, the potential loss of this protection in the setting of the dual use of COX-2 inhibitors with aspirin or over-the-counter NSAIDs remains underappreciated by clinicians.

GI Effects of Aspirin in Patients Receiving a Coxib versus Traditional NSAID Therapy

Although no controlled outcome studies have been performed specifically to assess patients receiving aspirin in combination with a coxib or a traditional NSAID, mounting evidence suggests that there is no GI safety advantage for coxib versus traditional NSAID therapy in this setting. In trials that compared celecoxib with other NSAIDs on the incidence of endoscopically detected ulcers in patients not receiving aspirin and those receiving aspirin doses of up to 325 mg/day, the reduction in ulcer risk with celecoxib versus other NSAIDs was significant only among those not receiving aspirin. In the Celecoxib Long-Term Arthritis Safety Study (CLASS),[6] celecoxib (400 mg twice daily) was compared with ibuprofen (800 mg 3 times daily) or diclofenac (75 mg twice daily) in patients with osteoarthritis (72% of patients) or rheumatoid arthritis (28% of patients). The reported 6-month data revealed that treatment with celecoxib significantly decreased GI symptoms, including abdominal pain, dyspepsia, and nausea ($P < .05$), as well as reducing rates of ulcer complications and symptomatic ulcers ($P = .02$). Importantly, however, among the 21% of patients receiving concurrent aspirin therapy, there were no statistically significant differences between those receiving celecoxib and those receiving a traditional NSAID in ulcer complications ($P = .92$) or all ulcers ($P = .49$). This post hoc underpowered analysis was the first strong signal that the use of concomitant aspirin likely offsets the gastroprotective effect of coxibs (Figure 2).

The TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial) study[7] compared lumiracoxib with naproxen and ibuprofen in more than 18,000 patients, 24% of whom were taking aspirin, over a 52-week period. There was a significant reduction in ulcer complications in the entire population (relative risk [RR], 0.34; 95% confidence interval [CI], 0.22-0.52), but not in the subgroup taking aspirin (RR, 0.79; 95% CI, 0.40-1.55).

Given the integrated body of data demonstrating that concomitant aspirin and coxib use creates ulceration at a rate similar to that of a dual inhibitor, clinical decision making should mandate strategies to reduce that risk in appropriate patients. Further, because aspirin use is a marker of CV risk, the use of coxibs in such patients should be a concern not only from the GI but from the CV perspective.

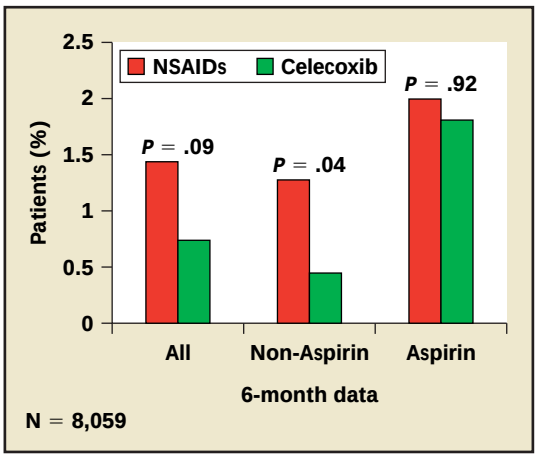


Figure 2. *The effect of concomitant low-dose aspirin use on gastrointestinal (GI) toxicity (symptomatic upper GI ulcers and ulcer complications) in 8059 patients with osteoarthritis or rheumatoid arthritis receiving celecoxib (400 mg twice daily) or nonsteroidal anti-inflammatory drugs (NSAIDs): the CLASS study.[6] Adapted with the permission of the American Medical Association.*

Prevention of GI Ulcers and Complications

As prostaglandin depletion is the central mechanism for NSAID-induced ulcer development, replacement therapy with the synthetic prostaglandin misoprostol reduces NSAID toxicity. Although it is the only US Food and Drug Administration–approved regimen for prevention of NSAID ulcers *and* complications, it is rarely used, due to side effects of diarrhea and abdominal cramping.

Sucralfate, a basic aluminum salt of sucrose octasulfate, forms an ulcer-adherent complex at duodenal ulcer sites, protecting the ulcer and promoting healing; sucralfate may also inhibit pepsin activity in gastric fluid. Sucralfate has been shown to be effective in the treatment of NSAID-associated duodenal ulcers, particularly when the NSAID use is stopped, but is not effective in the treatment or prevention of NSAID-related gastric ulcers. Its use is not recommended, given the availability of far superior therapeutic choices.

The level of acid suppression provided by traditional doses of

H_2-receptor antagonists (H_2RAs) does not prevent most NSAID-related gastric ulcers. Despite a single endoscopic study demonstrating that H_2RAs at double the traditional dose may be effective compared with placebo, no studies comparing high doses of H_2 blockers with misoprostol or proton-pump inhibitors (PPIs) for the prevention of NSAID ulcers are available. Given compliance concerns with twice-daily dosing, PPI therapy is the rational alternative to H_2RAs in this clinical setting. PPIs have proven superior to both ranitidine and misoprostol in preventing NSAID-associated ulcer recurrence and in producing overall symptom control, largely related to their ability to reduce ulcers and improve NSAID-associated dyspepsia, thereby improving overall quality of life.[8]

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Dyspepsia

Up to 40% of those treated with full-dose NSAIDs experience UGI symptoms such as dyspepsia, abdominal pain, and heartburn. Similar rates are seen in those taking aspirin, particularly at doses greater than 325 mg daily. Although the frequency of such symptoms is less at lower aspirin doses, they can still be problematic for many patients. These symptoms can have a marked effect on quality of life and may be sufficiently severe to necessitate dose interruption or discontinuation of therapy.

Acid suppression seems to be a highly successful approach to reducing such dyspeptic side effects. In a recently published trial,[9] esomeprazole at a dose of 20 mg or 40 mg was effective for treating UGI symptoms, whether based on patient reports of upper abdominal pain, burning, or discomfort or on investigators' assessments of heartburn and acid regurgitation. Esomeprazole was well tolerated, and both doses of esomeprazole produced faster symptom relief and an increased number of symptom-free days than placebo. This was associated with a significant reduction in the use of antacid rescue medication in the esomeprazole treatment groups. While an H_2 blocker may be effective for this purpose, the improved compliance and the known efficacy of a PPI to reduce concomitant ulcer risk—a particular concern in a dyspeptic patient who is not going to undergo endoscopy—make this the clear choice for overall patient symptom control and ulcer prevention.

Strategies to Reduce the GI Risk of Low-Dose Aspirin

There are few high-quality prospective data to guide clinical decision making in the area of low-dose aspirin and other antiplatelet drugs. Extrapolation of data from NSAID trials seems rational, as an approach that works for a full-dose NSAID would likely provide a similar outcome with low-dose aspirin. For misoprostol, given the side effects and the uncertainty as to whether lower dosing will provide benefits in reducing the risks of low-dose aspirin, its use cannot be recommended. The use of an H_2RA may be of some value, based on short-term endoscopy studies and case-control studies, but given the proven efficacy and ease of administration of a PPI, this approach seems most prudent, albeit more costly.

Lai and colleagues[10] showed that treatment with a PPI prevented recurrent ulcer bleeding in high-risk patients taking aspirin. Patients with previous ulcer bleeding and *Helicobacter pylori* infection were first treated to eliminate the infection, then randomized to receive either lansoprazole (30 mg/day) or placebo, in addition to low-dose aspirin therapy. The percentage of patients with recurrent ulcer complications after 1 year was significantly lower in the lansoprazole-treated group (1.6%) than in the placebo group (14.8%; $P = .008$) (Figure 3).

The safety of reinitiating antiplatelet therapy in the setting of recent GI bleeding (usually due to

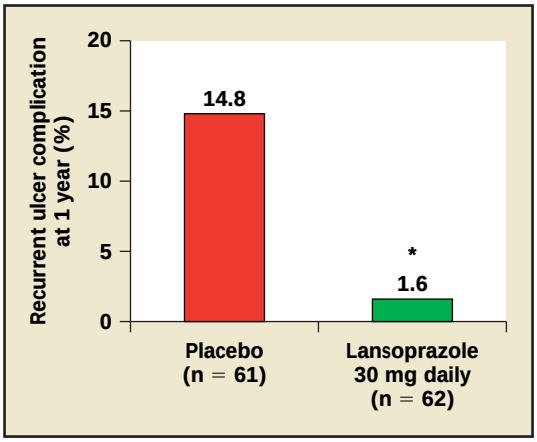

Figure 3. *Lansoprazole for prevention of recurrent ulcer complications in patients taking low-dose aspirin. Four of 9 patients with recurrent bleeding had recurrent* H. pylori *infection, emphasizing the simplicity of proton-pump inhibitor treatment over attempts at curing* H. pylori *infection as the sole strategy to reduce the risks of aspirin. *P = .008. Data from Lai et al.*[10]

ulcer disease) is a frequent clinical conundrum. In general, the overriding concern should be the need for the antiplatelet drug and the likelihood of a serious adverse CV outcome if this treatment is stopped. In the setting of appropriate PPI therapy for ulcer healing, low-dose aspirin can generally be restarted for those patients who require it, following appropriate endoscopic treatment for bleeding. The concurrent use of anticoagulation may be problematic and should be evaluated on a case-by-case basis. Clearly, collaboration between the gastroenterologist and cardiologist is essential for improving patient outcomes and care, which should be individualized according to competing risks for bleeding versus thrombotic complications.

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Eradication of *H. pylori*

Ulcers related to NSAIDs and to *H. pylori* form by distinct mechanisms: NSAID ulcers occur without gastritis (the injury observed endoscopically has minimal microscopic inflammation), whereas *H. pylori* causes mucosal inflammation that is usually not evident by endoscopy. Given these different mechanisms, patients with a history of peptic ulcer disease should be tested for *H. pylori* and treated with antibiotics to reduce recurrence of *H. pylori*–associated ulcers. However, eradication of the infection alone is insufficient to reduce the much larger independent NSAID-associated ulcer risk.

Chan and colleagues[11] reported that, among patients with *H. pylori* infection and a history of UGI bleeding, omeprazole therapy was equivalent to eradication of *H. pylori* in preventing recurrence of bleeding due to low-dose aspirin therapy. However, the follow-up time in this study was relatively short (6 months), and there were twice as many ulcer recurrences in the eradication group alone as in the group receiving the PPI.

A number of case-control studies have shown that aspirin and *H. pylori* infection have at least an additive effect on the risk of UGI bleeding. *H. pylori* infection increases the risk of UGI bleeding in aspirin users 5-fold compared with aspirin use alone. Although *H. pylori* is a risk factor for GI bleeding, in the Lai study described earlier,[10] in the placebo group, around 15% of patients had recurrent ulcer bleeding despite treatment to eradicate their *H. pylori* infection. Further investigation shows that, of this group of patients, in almost 10% the eradication of *H. pylori* had failed, or they had taken concomitant NSAIDs, leaving only 5% who had recurrent aspirin-associated bleeding after successful *H. pylori* eradication.

To further address this issue, a prospective cohort study was undertaken, starting in Hong Kong in 1996, to quantify the incidence of UGI bleeding in different populations of aspirin users: (1) average-risk aspirin users (no history of ulcer disease; aspirin-naive), (2) those with previous aspirin-associated GI bleeding and an eradicated *H. pylori* infection, and (3) those with previous aspirin-associated GI bleeding and no previous *H. pylori* infection.[12] Patients were treated with low-dose aspirin (80-100 mg/day) without a gastroprotective agent and were followed up regularly for 4 years. The cumulative incidence of UGI bleeding in these 3 groups was 2.0%, 4.5%, and 18.4%, respectively, giving an annualized incidence of 0.5%, 1.1%, and 4.6%, respectively. Thus it seems that the eradication of *H. pylori* infection can substantially reduce the risk of recurrent ulcer complications in high-risk aspirin users, to the rate seen in low-risk patients.[12]

Diagnosis and Treatment of H. pylori

Most cardiologists are unlikely to be familiar with the diagnosis and treatment of *H. pylori* infection and may want to refer the patient to a clinician familiar with this area. Noninvasive *H. pylori* testing is currently recommended for patients who do not need endoscopy. Two general categories of noninvasive *H. pylori* tests are now available: those that identify active infection and those that detect antibodies (exposure). This distinction is important because antibodies (ie, a positive immune response) indicate only the presence of *H. pylori* at some time: antibody tests do not differentiate between previously eradicated *H. pylori* infection and currently active *H. pylori*. Compared with tests for active infection, tests for antibodies are simpler to administer, provide a faster result, and are less expensive. However, the probability that a positive antibody test reflects active infection decreases as the proportion of patients with previously eradicated *H. pylori* increases. Successfully treated patients include both those given antibiotics specifically for an *H. pylori* infection and those with undiagnosed *H. pylori* who received antibiotics for another infection, and these antibiotics also eradicated the *H. pylori*; less common is spontaneous eradication of *H. pylori* infection.[14]

Helicobacter pylori serologic tests detect antibodies to *H. pylori* with a sensitivity and specificity of approximately 90%. In populations with low disease prevalence, the positive predictive value of the test falls dramatically, leading to unnecessary treatment. Office-based serologic tests are less accurate than laboratory-based ELISA tests; the office-based tests have the advantage of providing a result within half an hour. Serology tests should be used only for initial diagnosis of *H. pylori*, because, as noted above, antibody levels often remain elevated after *H. pylori* is eliminated. Serology tests should not be used for a patient who has been treated for *H. pylori* to confirm a cure.

Tests for Active H. pylori *Infection*

Tests for active *H. pylori* include fecal *H. pylori* antigen testing and urea breath testing. The stool antigen test has been reported to have a sensitivity and specificity of more than 90% in untreated patients with suspected *H. pylori* infection. The test requires a patient stool sample the size of an acorn, collected by either the clinician or the patient. This test must be performed in a laboratory by trained personnel.

For the urea breath test, the patient drinks an oral preparation containing ^{13}C- or ^{14}C-labeled urea. *H. pylori* in the stomach metabolizes this urea; the carbon is absorbed into the bloodstream, travels to the lungs, and is exhaled as carbon dioxide. The isotope-labeled carbon dioxide is measured to determine the presence or absence of *H. pylori*. This test has a sensitivity and specificity of more than 90% for active infection. However, the test requires more patient preparation and is more expensive. A number of drugs can adversely affect the accuracy of urea breath tests. Before testing, antibiotics and bismuth should be withheld for at least 4 weeks, PPIs should be withheld for at least 7 days, and patients should fast for at least 6 hours.

Treatment of H. pylori

The choice of therapy should consider the effectiveness and cost of various regimens versus side effects. PPIs have in vitro activity against *H. pylori*.

The probability that a positive antibody test reflects active infection decreases as the proportion of patients with previously eradicated H. pylori *increases.*

A combination of PPI plus clarithromycin plus either amoxicillin or metronidazole has demonstrated impressive eradication rates when used for 10 to 14 days. Amoxicillin is preferred for patients who have previously been treated with metronidazole. Metronidazole is preferred for patients allergic to penicillin. "Bismuth-based triple therapy" is a less costly alternative: Pepto-Bismol (2 tablets 4 times daily), metronidazole (250 mg 4 times daily), and tetracycline (500 mg 4 times daily) for 2 weeks is the best-studied, highly effective anti–*H. pylori* therapy (≥ 85% eradication). The duration and multidrug nature of this regimen, usually given with an H_2-receptor antagonist or PPI, have been associated with decreased compliance, leading to potential failure to eradicate the *H. pylori* infection.[14]

The complexity of testing and treatment of *H. pylori* infection, despite its apparent value as sole therapy to reduce risk, supports the superiority of PPI therapy alone for its simplicity and efficacy, even for *H. pylori*–infected patients, as demonstrated by the Lai study.[10]

Use of an Alternative Antiplatelet Agent

One option that can be considered to reduce aspirin-associated GI complications is switching to other antiplatelet agents. The American College of Cardiology/American Heart Association guidelines currently recommend use of clopidogrel for hospitalized patients who cannot take aspirin because of major GI intolerance. A double-blind, randomized study was undertaken in 320 patients with coronary heart disease or stroke who had previous ulcer bleeding; all ulcers were fully healed before participation in the trial.[13] After 1 year of treatment with clopidogrel, 8.6% of patients had recurrent UGI bleeding, compared with only 0.7% of those treated with a combination of aspirin plus PPI (Figure 4). These results suggest that clopidogrel should not be used *alone* as an alternative to aspirin plus PPI for patients at risk of ulcers.

Study results suggest that clopidogrel should not be used alone *as an alternative to aspirin plus proton-pump inhibitor for patients at risk of ulcers.*

These prospective data support an observational study that among a cohort of patients with prior ulcer who took clopidogrel, 12% had recurrent bleeding at 1 year. These same investigators found that adding omeprazole to either aspirin or clopidogrel was a successful approach to reducing risk in a nonplacebo-controlled trial.[13]

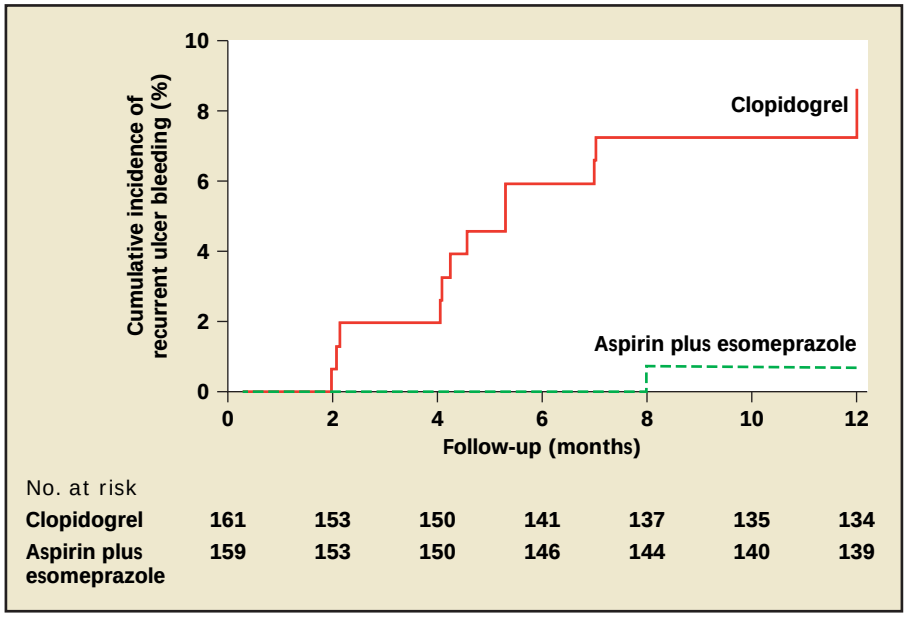

Figure 4. *Antiplatelet therapy versus aspirin plus proton-pump inhibitor: cumulative incidence of recurrent ulcer bleeding. P = .001. Reprinted with permission from Chan et al.*[13]

The Future

The addition of nitric oxide to aspirin or other NSAIDs is showing promise as a way to improve the GI tolerability of NSAIDs. Experimental studies have demonstrated that nitric oxide donors decrease NSAID-induced gastric damage, and administration of nitric oxide–NSAIDs induces little or no damage to the GI mucosa, while maintaining the anti-inflammatory properties of the NSAID. Adding further support to this hypothesis is the finding from recent epidemiological studies that nitrovasodilator therapy is associated with a 40% to 60% reduction in the risk of UGI bleeding in patients taking NSAIDs, including aspirin.[15] Clinical studies of at-risk patients are eagerly awaited. ■

Main Points

- Despite the therapeutic benefits for primary and secondary prevention of cardiovascular disease, even low doses of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk for gastrointestinal (GI) side effects. As only 1% to 2% of chronic aspirin users develop a symptomatic ulcer, and risk varies considerably across individuals, it is essential to assess individual patient risk for complications.
- The US Preventive Services Task Force recommends a risk-benefit calculation before prescribing low-dose aspirin for primary prevention of cardiovascular events; it recommends prophylactic aspirin only for those with a 3% or greater 5-year risk of such events.
- The 2-fold greater risk of GI bleeding for those taking chronic low-dose aspirin compared with those not taking aspirin is not reduced by enteric coating or by the use of buffering, as the toxicity is due to the systemic absorption of aspirin; thus, even transcutaneous aspirin may cause a bleeding ulcer.
- Taking both cardioprotective aspirin (primarily a cyclooxygenase [COX]-1 inhibitor at low doses) and a COX-2 inhibitor creates the same ulcer risk as a traditional NSAID.
- Proton-pump inhibitors (PPIs) have proven superior to both ranitidine and misoprostol in preventing NSAID-associated ulcer recurrence and in producing overall symptom control.
- Although an H_2 blocker may be effective for treating NSAID-associated dyspepsia, the improved compliance and the known efficacy of a PPI to reduce concomitant ulcer risk make this the clear choice for symptom control and ulcer prevention.
- In judging the safety of reinitiating antiplatelet therapy in the setting of recent GI bleeding, the overriding concern should be the need for the antiplatelet drug and the likelihood of a serious adverse cardiovascular outcome if this treatment is stopped.
- Eradication of *H. pylori* infection can substantially reduce the risk of recurrent ulcer complications in high-risk aspirin users.
- For patients with prior bleeding due to aspirin, clopidogrel is not a safer alternative. It caused more bleeding than aspirin plus a PPI in a high-risk cohort of patients.

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