Upper GI Risks of NSAIDs and Antiplatelet Agents: Key Issues for the Cardiologist

David A. Johnson, MD, FACP, FACG

Division of Gastroenterology, Eastern Virginia Medical School, Norfolk, VA

The use of antiplatelet/antithrombotic agents (eg, low-dose aspirin or clopidogrel) in primary or secondary intervention treatment strategies for cardiovascular disease is a common practice among cardiologists. Furthermore, these agents frequently are used concomitantly with other nonsteroidal anti-inflammatory drugs (NSAIDs) that patients are taking for a wide array of rheumatologic- or orthopedic-related complaints. These therapies, however, have defined upper gastrointestinal (UGI) risks for ulcer-related injury and complications. It is important for the cardiologist to fully understand the UGI risk profiles so that each patient is evaluated as a candidate for possible preventive co-therapy with appropriate anti-ulcer medication.

[Rev Cardiovasc Med. *2005;6(suppl 4):S15-S22*]

Key words: NSAIDs • Upper gastrointestinal bleeding • Peptic ulcer • Low-dose aspirin • Antithrombotic agents • Antiplatelet agents • Clopidogrel • *Helicobacter pylori*

The untoward consequences of nonsteroidal anti-inflammatory drug (NSAID) and antiplatelet therapies have become an area in need of increased clinical attention. Over the past 2 to 3 decades, NSAIDs have been recognized as one of the most important causes of upper gastrointestinal (UGI) bleeding.[1] Several management strategies have been adopted to prevent serious complications, including prophylactic anti-ulcer therapy and the use of "milder"

conventional NSAIDs or the selective use of cyclooxygenase-2 (COX-2) inhibitors.[2] These various management strategies, however, have been complicated by the increasing use of low-dose aspirin and other antithrombotic agents for cardiovascular protection. As such, it has become increasingly important that each patient be evaluated for exposure risk before implementing any of these interventional strategies.

The purpose of this review is to focus on the patient's interaction with the cardiologist. The key areas addressed are the prevalence of NSAID use, the consequences of GI injury due to selective and nonselective NSAIDs, the risk associated with a cardiac dose of aspirin, the risk of use of clopidogrel, the costs of NSAID-related UGI injury, and defining patient risk profiles when considering prophylactic therapy to reduce GI toxicity.

Prevalence of NSAID Use

The use of NSAIDs, including aspirin, is common in the treatment of pain, inflammation, and fever, and low-dose aspirin is frequently used for the prophylaxis of cardiovascular events. These agents are probably the most widely used medications in the United States. Population-based studies have shown a high prevalence of usage. Not surprisingly, NSAID use is increased among the elderly. In a survey of people aged 65 years or older, 70% used NSAIDs at least once weekly and 34% used them at least daily. The prevalence of at least weekly aspirin usage was 60%.[3] Even with the current decline in NSAID prescriptions, more than 111 million NSAID/COX-2 prescriptions were written in 2004, 45% of which were for a COX-2 selective agent. The total NSAID prescription market amounts to approximately $6.6 billion in annual drug costs.[4]

In 1990, the estimated prevalence of self-reported arthritis in the United States was 37.9 million cases, or 15% of the population. When this prevalence is applied to the 1995 estimated US population, the number of cases had increased to approximately 40 million by that year. By 2020, it is projected that 59.4 million Americans will be affected by arthritis, a 57% increase from 1990.[5]

Currently, approximately 2 million patients with arthritis use NSAIDs for symptom relief.[2] As the prevalence of rheumatoid arthritis increases, chronic NSAID use is also expected to increase.[6]

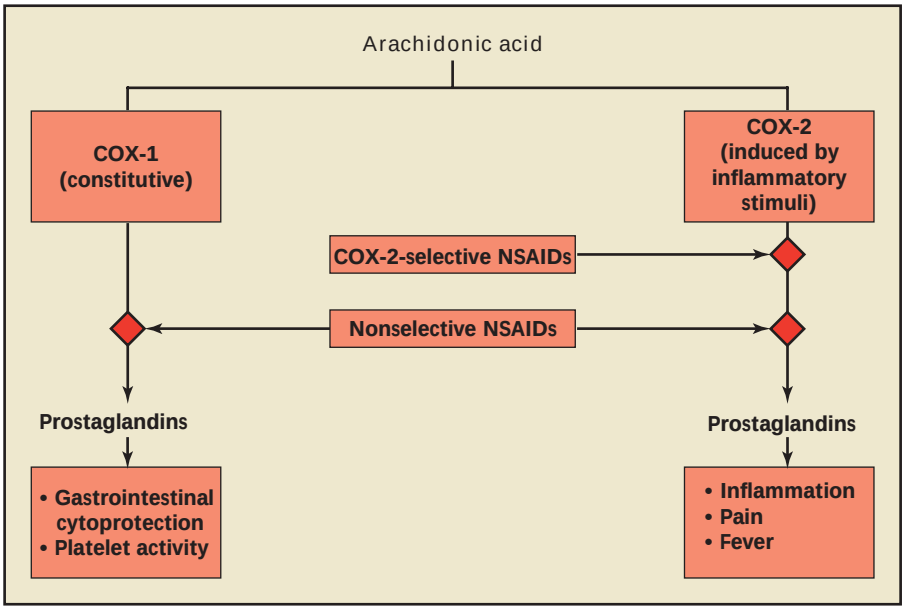
Mechanisms of GI Injury

Tissue prostaglandins (PGs) are produced via 2 pathways, a COX-1 pathway and a COX-2 pathway (Figure 1). The PGs that are inhibited when the COX-1 pathway is blocked are responsible for protecting the GI mucosa and play an important protective role in the stomach by increasing mucosal blood flow and stimulating the synthesis and secretion of mucus and bicarbonate. Inhibition of PGs causes decreases in protective factors such as epithelial mucus, secretion of bicarbonate, mucosal blood flow, and epithelial proliferation. This systemic PG-mediated effect is thought to be the most important mechanism of NSAID-induced side effects.[7] NSAIDs block the production of bicarbonate, mucus, and prostaglandins, eliminating 3 important factors that normally protect the gastric mucosa. This leads to an acidic environment and a weaker mucosal membrane, which may be more susceptible to topical attack by endogenous factors (acid, pepsin, and bile salts) (Figure 2).

GI-Related Complications of NSAIDs

Nonselective NSAIDs account for about 20% of all reported drug-related adverse events in the United States and approximately 25% in the United Kingdom.[6] In the United States alone, NSAID use has been

Figure 1. *Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX). NSAID-mediated inhibition of prostaglandin synthesis is the central mechanism behind both the therapeutic and toxic activity of NSAIDs. Adapted from Vane JR, Botting RM.* Inflamm Res. *1995;44:1-10.*



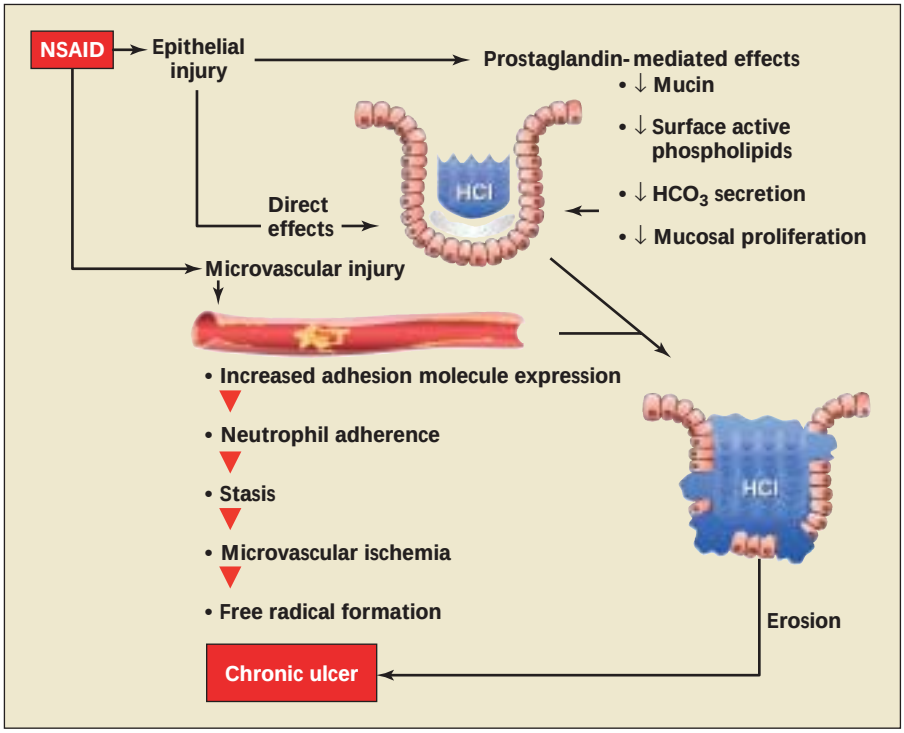


Figure 2. *The pathogenesis of nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers occurs through both the direct topical effects on the mucosa and the systemic effects of prostaglandin inhibition. Reprinted with permission from Scheiman.*[7]

conservatively estimated to account for approximately 107,000 hospitalizations and 16,500 deaths per year among patients with arthritis (of an estimated 13 million arthritis patients exposed to NSAIDs)—considerably greater than the number of deaths from conditions such as multiple myeloma, asthma, cervical cancer, or Hodgkin's disease. In fact, if deaths resulting from NSAID-associated UGI complications were tabulated separately, they would represent the 15th most common cause of death in the United States.[8,9]

If deaths resulting from NSAID-associated upper GI complications were tabulated separately, they would represent the 15th most common cause of death in the United States.

It is important for physicians to understand the incidence of UGI ulcers caused by NSAID use. After a single dose of a nonselective NSAID, almost all patients develop some degree of gastric erosion, and approximately 10% to 30% of chronic users develop an ulcer, with the prevalence of gastric ulcers approximately twice that of duodenal.[10,11] There is an important distinction between typical peptic ulcers and NSAID-associated ulcers, as only 30% of patients with NSAID-induced ulcers develop symptoms.[10] Therefore, it is extremely important for physicians and their patients taking NSAIDs to remember that symptoms are not a reliable indicator of the presence or absence of NSAID-related ulcers.

NSAID-associated ulcers range in severity from endoscopically visible ulcers that are frequently asymptomatic to the life-threatening complication of a perforated or bleeding ulcer. Additionally, the healing of preexisting ulcers is delayed by the continued use of nonselective and COX-2–selective NSAIDs.[12]

Effects of "Cardiac Dose" Aspirin

Aspirin prevents thromboses and blocks platelet aggregation through inhibition of the cyclooxygenase enzyme, thereby reducing thromboxane synthesis. Owing to the inhibition of cyclooxygenase in the GI tract, aspirin also causes gastrointestinal ulceration and major bleeding, which limit its usefulness as an antithrombotic agent.

The risk of GI bleeding generally increases by a factor of 2 to 3 with the use of low-dose aspirin.[13] A large population-based study in Denmark reported an annual incidence of UGI bleeding of 0.6% in patients taking low-dose "cardioprotective" aspirin, compared with a 0.24% "background rate" in patients not using NSAIDs or aspirin.[14] A systematic review of epidemiologic studies has shown that patients taking thrombo-prophylactic doses of aspirin, 75 mg daily, have a 2-fold increased risk of UGI complications compared with those not taking aspirin, and the risk is further increased with the use of analgesic/anti-inflammatory doses of 150 to 300 mg daily. Adding aspirin to another nonselective NSAID results in an 8-fold increased risk compared with the NSAID alone (Figure 3). Furthermore, the relative risk associated with aspirin is not reduced by buffered and enteric-coated formulations.[15]

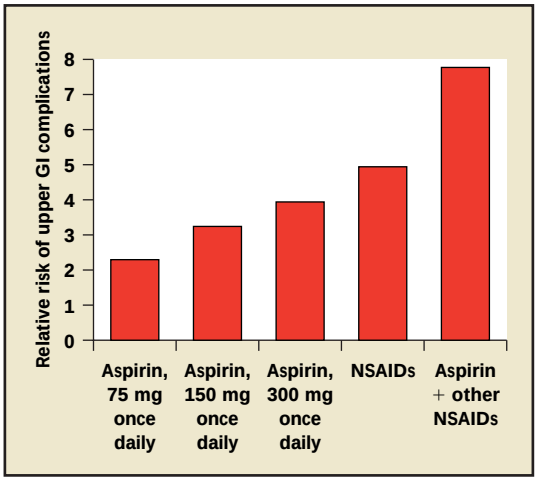


Figure 3. *Aspirin, alone or with another nonsteroidal anti-inflammatory drug (NSAID), and risk of upper gastrointestinal (GI) complications. A systematic review of epidemiological studies has shown that patients taking thromboprophylactic doses of aspirin, 75 mg daily, present a 2-fold increased risk of upper GI complications compared with those not taking aspirin, and the risk is further increased with the use of analgesic/anti-inflammatory doses of 150–300 mg daily. Adding aspirin to another nonselective NSAID results in an 8-fold increase in risk compared with not adding aspirin. Furthermore, the relative risk associated with aspirin is not reduced by buffered and enteric-coated formulations. Data from Weil et al.*[15]

Although the gastrointestinal risks associated with aspirin can be reduced by decreasing the dose to the lowest effective amount, even the lowest doses have considerable risks: 75 mg daily doubles the risk of GI bleeding, and even the subtherapeutic dose of 10 mg daily substantially inhibits gastric cyclooxygenase and still causes gastric ulceration.[16] Thus, it is unlikely that there is a daily dose of aspirin that has antithrombotic efficacy without gastrointestinal risks.

Effects of Clopidogrel

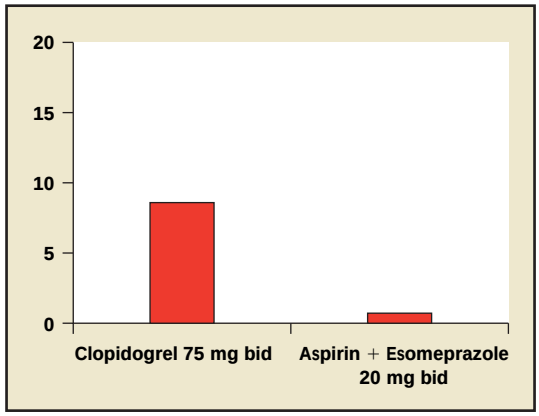
A common clinical dilemma is how best to treat patients who need antiplatelet therapy but are also at high risk for GI bleeding, an example being patients with a recent history of UGI bleeding induced by aspirin or other NSAIDs. Current cardiology guidelines recommend clopidogrel for patients unable to take aspirin because of previous gastrointestinal intolerance.[17] Clopidogrel is an effective antithrombotic agent because it blocks the platelet activation of adenosine diphosphate (ADP) by irreversibly binding to the ADP receptors of platelets. This prevents the ADP-dependent activation of the glycoprotein IIb/IIIa complex, the primary platelet receptor for fibrinogen.

Conventional wisdom suggests that clopidogrel should be a safer, non-ulcerogenic alternative for patients at high risk for aspirin-induced ulcers, because it does not affect mucosal prostaglandin production. Surprisingly, for those at highest risk because of a history of GI bleeding, the risk of subsequent bleeding with the use of clopidogrel is not diminished. For example, one study demonstrated that a history of GI bleeding was an important risk factor for GI bleeding during treatment with clopidogrel.[18] In a randomized, prospective study of the efficacy of 75 mg of clopidogrel versus 325 mg of aspirin given daily for the secondary prevention of thrombotic vascular events, clopidogrel was only marginally more effective than aspirin and resulted in only a moderately lower rate of GI bleeding (0.5% vs 0.7%).[19] In endoscopic evaluations of healthy volunteers at 1 week, clopidogrel caused less gastroduodenal damage than did 325 mg of aspirin given daily.[20]

A recent prospective randomized study, performed in Hong Kong, looked at patients who took aspirin to prevent vascular diseases and who presented with ulcer bleeding.[21] After the ulcers had healed, patients who were negative for *Helicobacter pylori* were randomized to receive either 75 mg of clopidogrel daily plus an esomeprazole placebo twice daily or 80 mg of aspirin daily plus 20 mg of esomeprazole twice daily for 12 months. Over a 1-year follow-up period, the patients in the group receiving clopidogrel had a significant increase in the rate of recurrent UGI bleeding from ulcers, compared with those in the group taking aspirin plus esomeprazole (8.6% vs 0.7%, $P = .001$) (Figure 4).

The impairment of ulcer healing by clopidogrel has not been widely appreciated. Platelet aggregation plays a critical role in healing, through the release of various platelet-derived growth factors that promote angiogenesis, which is essential for ulcer healing. For example,

Figure 4. *Probability of recurrent ulcer bleeding (percent), clopidogrel versus aspirin plus esomeprazole. Esomeprazole 20 mg bid is an off-label dose. Data from Chan et al.*[21]



experimental animals with thrombocytopenia have reduced ulcer angiogenesis and impaired healing of gastric ulcers.[22] ADP-receptor antagonists impair the healing of gastric ulcers by inhibiting the release by platelets of pro-angiogenic growth factors such as vascular endothelial growth factor, which promotes endothelial proliferation and accelerates the healing of ulcers. Additionally, GI bleeding is a major toxic effect of chemotherapeutic regimens that use monoclonal antibodies directed at circulating vascular endothelial growth factor.[23] Although clopidogrel and other agents that impair angiogenesis might not be the primary cause of GI ulcers, their anti-angiogenic effects may impair the healing of background ulcers. By this effect, when combined with the propensity to increase bleeding, these agents may convert small, silent ulcers into large ulcers that bleed.

Although clopidogrel and other agents that impair angiogenesis might not be the primary cause of GI ulcers, their anti-angiogenic effects may impair the healing of background ulcers.

Balancing the Risk-Benefit Profiles of Low-Dose Aspirin and Antithrombotic Drugs

It is clear that NSAIDs, including cardiac doses of aspirin, as well as other antithrombotic drugs are associated with UGI ulcerations and hemorrhage. The cardiologist needs to understand these factors in order to best balance the risk-benefit profile for patients at risk. A recent 6-year analysis of UGI bleeding associated with the use of low-dose "cardioprotective" aspirin and antithrombotic drugs provides a good perspective for this understanding.[24] In this European study, the incidence of UGI bleeding per 100,000 patients rose from 15 in 1996, to 18 in 1999, to 27 in 2002 ($P = .004$). Over that same time, the number of prescriptions for low-dose aspirin rose from 209 (1996) to 367.6 per 1000 (2002). Similarly, over the same time period, the incidence of UGI bleeding associated with other antithrombotic use also increased significantly ($P < .001$), from 3.5 (1996) to 7.8 (1999) to 12.1 (2002) per 100,000 patients. During this same time, the number of prescriptions for antithrombotic agents rose from 222 (1996) to 433 (2002) per 1000 patients, and for clopidogrel specifically, the prescription rates increased from 0 (1996) to 31.3 (2002) per 1000. The "trade-off" however, was a significant decline in mortality due to acute myocardial infarction, from 215 (1996) to 13.7 (2002) per 100,000. Clearly the use of low-dose aspirin and antithrombotic drugs has had a dramatic impact—both good and bad.

Role of *Helicobacter pylori*

Helicobacter pylori infection and NSAID use synergistically increase the risk of peptic ulcer disease. Infection with *H. pylori* is known to be a major cause of peptic ulcer disease. The results of a meta-analysis showed an increase in ulcer occurrence and bleeding in patients with *H. pylori* infection who also used NSAIDs,[25] indicating the synergy between *H. pylori* infection and the use of NSAIDs in damaging the gastroduodenal mucosa. Accordingly, peptic ulcer disease was significantly more common in patients taking NSAIDs than in controls, irrespective of *H. pylori* infection (Figure 5). Peptic ulcer disease in NSAID users, however, was found to be significantly more common among those infected with *H. pylori* than in those free from the infection. In case-control studies, the risk of developing a peptic ulcer was 61 times greater among *H. pylori*–positive NSAID users than among *H. pylori*–negative individuals not taking NSAIDs. Additionally, *H. pylori* infection and NSAID use were found to increase the risk of ulcer bleeding 1.79-fold and 4.85-fold, respectively. When both factors were present, the risk of ulcer bleeding increased 6.13-fold.

The role of *H. pylori* is an independent yet additive factor in NSAID-related UGI injury. As such, patients who are found to have an ulcer should be screened for *H. pylori* and

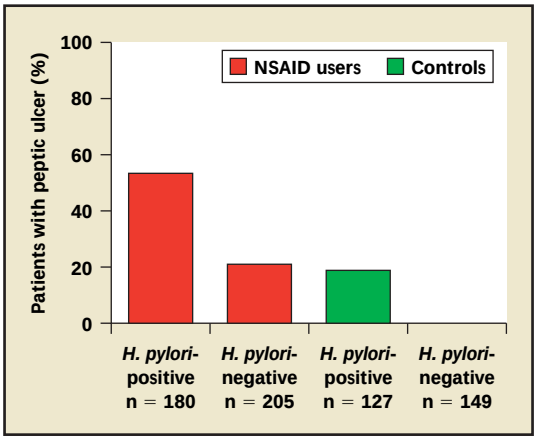


Figure 5. Helicobacter pylori *and nonsteroidal anti-inflammatory drug (NSAID) use are independent but additive risk factors for peptic ulcer disease. Reproduced with permission from Huang et al.*[25]

appropriately treated. There are no current standards, however, that endorse screening for *H. pylori* in patients who are to be treated with NSAIDs or antithrombotic therapies.

Costs of NSAID GI-Related Complications

The increased incidence of upper gastrointestinal complications associated with NSAID use represents a substantial demand on health care resources, with significant medical costs incurred by treating these side effects. Conservative estimates suggest that the cost of each hospitalization for NSAID-related ulceration is approximately $15,000 to $20,000. With 107,000 hospitalizations for serious UGI complications in the United States each year, the annual cost exceeds $2 billion.[6]

These costs associated with NSAID use were highlighted in a study of more than 75,000 people in the United States, aged 65 years or older, that calculated the annual rates of utilization of, and payments for, medical care for NSAID-associated UGI disorders, including hospitalization and emergency department visits for peptic ulcers, gastritis/duodenitis, and UGI bleeding; outpatient upper and lower GI radiologic and endoscopic examinations; and acid-suppressive drugs.[26] The mean annual payment for the medical care of gastric disease in non-NSAID users was $134 per patient; however, for users of nonselective NSAIDs this figure increased by $57 (43%) to $191. The excess cost associated with NSAID use increased with the dose of NSAID taken. Excess cost was $56 for patients taking less than 1 standard dose of nonselective NSAID per day, but this rose to $120 for those taking 1 to 2 standard doses, and $157 for patients taking more than 2 standard doses per day.

Defining the Patients at Risk

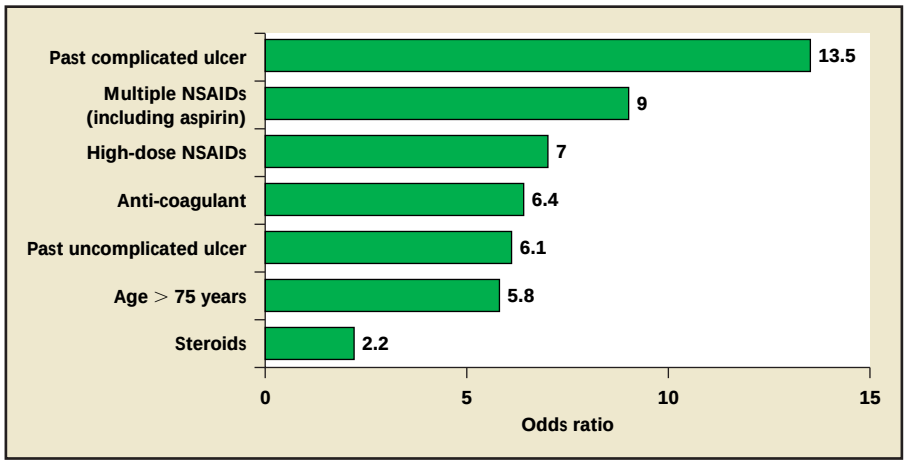
Gastric ulcers associated with use of NSAIDs may progress to complicated ulcer disease if left untreated or undiagnosed. To reduce the magnitude of the problem, physicians need to understand that certain patients are at a predictably higher risk of NSAID-related GI morbidity/mortality than others. A number of studies have identified patient groups that are more likely to experience adverse GI consequences with NSAID therapy.[6,26-30] Advanced age has been identified as one of the primary risk factors; others include previous complications of ulcers, higher doses of NSAIDs, use of multiple NSAIDs (including cardioprotective aspirin), previous ulcer history, use of corticosteroids, or concomitant anticoagulant use (Figure 6). It is important to understand that the addition of low-dose aspirin to another NSAID creates a significant risk factor: multiple NSAID use. Studies have demonstrated that the addition of low-dose aspirin to a "safer" selective COX-2 inhibitor essentially nullifies the "lower ulcer risk" profile of the selective inhibitor and puts the risk for NSAID-related UGI injury at the level of that for a traditional nonselective NSAID.[31] The key point is to define the risk for each patient before initiation of NSAID or antithrombotic therapy. Obtaining a careful medical history, with specific questioning about the concomitant use of over-the-counter NSAIDs, is critically important in defining the risk-benefit profile for each patient.

Addition of low-dose aspirin to a "safer" selective COX-2 inhibitor essentially nullifies the "lower ulcer risk" profile of the selective inhibitor and puts the risk for NSAID-related upper GI injury at the level of that for a traditional nonselective NSAID.

Conclusions

The cardiologist is in a unique position to have a dramatic effect on the morbidity/mortality of patients with cardiovascular disease. Therapies for

Figure 6. *Risk factors for nonsteroidal anti-inflammatory drug (NSAID)-associated ulcer complications. The majority of patients who develop a serious gastrointestinal adverse event while taking NSAIDs are asymptomatic before the event. The risk is greatest in the first 3 months of use. Data from Garcia Rodriguez and Jick,[27] Gabriel et al.,[28] and Silverstein et al.[30]*



prevention of complications can be either primary or secondary (after an event or as a therapeutic intervention). The use of low-dose aspirin and other antithrombotic therapies has typically been part of these cardioprotective preventive strategies. Despite the recognizable benefits of these therapies, there is also a definable risk for development of UGI ulcers and related complications in these patients. There are, however, defined risk profiles that characterize patients at greatest risk for these complications. For cardiologists, a clear and thorough understanding of these risks is critical to optimize the overall treatment plan for their patients. Given that the ulcers associated with NSAIDs and antithrombotic therapies are typically asymptomatic (before a complication), the cardiologist cannot rely on a patient developing GI symptoms to herald the onset of an ulcer. Accordingly, the cardiologist should be proactive, defining the risk profile for each patient being evaluated for NSAID, antithrombotic, and/or anticoagulant therapy. Patients defined as at risk for related UGI injury should be considered candidates for prophylactic co-therapy with appropriate anti-ulcer medication. ■

References

1. Langman MJ. Adverse effects of conventional non-steroidal anti-inflammatory drugs on the upper gastrointestinal tract. *Fundam Clin Pharmacol.* 2003;17:393-403.
2. Hawkey CJ, Langman MJ. Non-steroidal anti-inflammatory drugs: overall risks and management. Complementary roles for COX-2 inhibitors and proton pump inhibitors. *Gut.* 2003;52:600-608.
3. Talley NJ, Evans JM, Fleming KC, et al. Non-steroidal anti-inflammatory drugs and dyspepsia in the elderly. *Dig Dis Sci.* 1995;40:1345-1350.
4. IMS National Prescription Audit Plus, 2004 (Jan. 2004–Dec. 2004).
5. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum.* 1998;41: 778-799.
6. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol.* 1999;26(suppl 56):18-24.
7. Scheiman JM. NSAIDs, gastrointestinal injury, and cytoprotection. *Gastroenterol Clin North Am.* 1996;25:279-298.
8. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med.* 1999;340: 1888-1899.
9. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med.* 1998;105(1B):31S-38S.
10. Larkai EN, Smith JL, Lidsky MD, Graham DY. Gastroduodenal mucosa and dyspeptic symptoms in arthritic patients during chronic nonsteroidal anti-inflammatory drug use. *Am J Gastroenterol.* 1987;82:1153-1158.
11. Laine L. Nonsteroidal anti-inflammatory drug gastropathy. *Gastrointest Endosc Clin N Am.* 1996;6:489-504.
12. Hawkey CJ, Karrasch JA, Szczepanski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. *N Engl J Med.* 1998; 338:727-734.
13. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ.* 2000;321:1183-1187.
14. Sorensen HT, Mellemkjaer L, Blot WJ, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol.* 2000;95:2218-2224.
15. Weil J, Colin-Jones D, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ.* 1995;310:827-830.
16. Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology.* 1999;117:17-25.

Main Points

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most important causes of upper gastrointestinal (UGI) bleeding. Management strategies, including prophylactic anti-ulcer therapy, use of "milder" conventional NSAIDs, or selective use of cyclooxygenase-2 (COX-2) inhibitors, have been complicated by the increasing use of cardioprotective low-dose aspirin and other antithrombotic agents.
- There is an important distinction between typical peptic ulcers and NSAID-associated ulcers, as only 30% of patients with NSAID-induced ulcers develop symptoms; symptoms are not a reliable indicator of the presence or absence of NSAID-related ulcers.
- The risk of GI bleeding generally increases by a factor of 2 to 3 with the use of low-dose aspirin. Adding aspirin to another nonselective NSAID results in an 8-fold increased risk compared with the NSAID alone.
- Even the lowest doses of aspirin have considerable risks: 75 mg daily doubles the risk of GI bleeding, and even a subtherapeutic dose of 10 mg daily substantially inhibits gastric cyclooxygenase and causes gastric ulceration.
- Conventional wisdom suggests that clopidogrel should be a safer, non-ulcerogenic alternative for patients at high risk for aspirin-induced ulcers because it does not affect mucosal prostaglandin production. For those at highest risk because of a history of GI bleeding, however, the risk of subsequent bleeding with the use of clopidogrel is not diminished.
- Cardiologists need to understand the role of NSAIDs, including cardiac doses of aspirin, and other antithrombotic drugs in causing UGI ulcerations and hemorrhage in order to best balance the risk-benefit profile for patients at risk.
- *Helicobacter pylori* infection and NSAID use synergistically increase the risk of peptic ulcer disease. Patients found to have an ulcer should be screened for *H. pylori* and appropriately treated.

17. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction–2002: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *Circulation*. 2002;106:1893-1900.
18. Ng FH, Wong SY, Chang CM, et al. High incidence of clopidogrel-associated gastrointestinal bleeding in patients with previous peptic ulcer disease. *Aliment Pharmacol Ther.* 2003;18: 443-449.
19. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet.* 1996;348:1329-1339.
20. Fort FT, Lafolie P, Toth E, Lindgarde F. Gastroduodenal tolerance of 75 mg clopidogrel versus 325 mg aspirin in healthy volunteers: a gastroscopic study. *Scand J Gastroenterol.* 2000;35: 464-469.
21. Chan FKL, Ching JYL, Hung LCT, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med.* 2005;352:238-244.
22. Ma L, Elliott SN, Cirino G, et al. Platelet modulate gastric ulcer healing: role of endostatin and vascular endothelial growth factor release. *Proc Natl Acad Sci U S A.* 2001;98:6470-6475.
23. Kabbinovar F, Hurwitz HI, Fehrenbaacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil/leucovorin with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol.* 2003;21:60-65.
24. Taha AS, Angerson WJ, Knill-Jones RP, Blatchford O. Upper gastrointestinal haemorrhage associated with low-dose aspirin and antithrombotic drugs—a 6 year analysis and comparison with non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther.* 2005;22:285-289.
25. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet*. 2002;359:14-22.
26. Smalley WE, Griffin MR, Fought RL, Ray WA. Excess costs from gastrointestinal disease associated with nonsteroidal anti-inflammatory drugs. *J Gen Intern Med.* 1996;11:461-469.
27. Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet.* 1994;343:769-772.
28. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. *Ann Intern Med.* 1991;115:787-796.
29. Fries JF, Williams CA, Bloch DA, Michel BA. NSAID-associated gastropathy: incidence and risk factor models. *Am J Med.* 1991;91:213-222.
30. Silverstein FE, Graham DY, Senior JR, et al. Misoprostil reduces serious gastrointestinal complications in rheumatoid arthritis: a prospective observational cohort study. *Arch Intern Med.* 1995;123:241-249.
31. Laine L. Proton pump inhibitor co-therapy with nonsteroidal anti-inflammatory drugs—nice or necessary? *Rev Gastroenterol Disord.* 2004;4(suppl 4):S33-S41.