Nonsteroidal anti-inflammatory drugs (NSAIDs) have become one of the most important drugs for relieving pain and reducing inflammation. It was reported that more than 111,000,000 prescriptions for NSAIDs were prescribed in the United States at a cost of $5 billion each year. Most NSAIDs derive their antipyretic, analgesic, and anti-inflammatory effects through inhibition of cyclooxygenase (COX), including COX-1 and COX-2, and hence the synthesis of prostaglandins. NSAIDs and other analgesic/antipyretic drugs such as acetaminophen might also act through inhibition of a newly discovered cyclooxygenase isoenzyme, COX-3, to reduce pain and possibly fever. In recent decades, aspirin has also been widely used for the prevention of cardiovascular disease. In addition, COX-2 inhibitors have the potential for chemoprevention of gastric and colorectal malignancies.

However, the anti-inflammatory and analgesic effects of NSAIDs are not obtained without cost. NSAIDs are an important cause of bleeding peptic ulcers in countries where the prevalence of *Helicobacter pylori* infection is decreasing. A recent study from Taiwan revealed that about 57.2% of patients with bleeding peptic ulcer reported recent use of NSAIDs or antiplatelet agents. NSAIDs that are selective for COX-2 inhibition (coxibs) are introduced to the market with popularity because they are associated with fewer gastrointestinal (GI) complications than non-selective NSAIDs. Unfortunately, rofecoxib and valdecoxib were withdrawn from the market because of their serious cardiovascular risks. Emerging data suggest that nonselective NSAIDs, except for naproxen, are also associated with increased risks for cardiovascular events. Thus, the choice of appropriate NSAIDs has become more complex than in previous practice.

**GI Toxicities: The Main Concern of NSAIDs**

GI intolerance is the most common adverse effect of NSAIDs, and a meta-analysis has revealed that NSAIDs increased the risk of dyspepsia by 36%. In the United States, NSAID-associated upper GI adverse events are estimated to result in 103,000 hospitalizations and 16,500 deaths per year. NSAID users had a 12.5 per 1000 person-years excess rate of ulcer-related hospitalization compared to non-NSAID users. A nationwide study of mortality associated with hospital admission due to severe GI events in Spain revealed that the death rate attributed to NSAID/aspirin use was...
15.3 deaths/100,000 NSAID/aspirin users, and that up to one third of all NSAID/aspirin deaths can be attributed to low-dose aspirin use. In an endoscopic evaluation of patients who had continuously used NSAIDs over the previous 6 months, gastroduodenal ulcers were detected in 24% of patients, and approximately 1–2% of NSAID users developed ulcer-related complications (bleeding, perforation, obstruction) annually. Notably, the majority of patients with NSAID-related GI complications did not have preceding abdominal symptoms. The first sign of an ulcer was a life-threatening complication in 58.2% of patients taking an NSAID.

Nonselective NSAIDs increase the risk of GI bleeding not only in the upper GI tract but also in the lower GI tract. Wilcox and Clark reported that the odds ratio (OR) for NSAID-associated upper and lower GI bleeding were 3.2 and 2.6, respectively. NSAID-related GI toxicities are related to direct irritation of GI mucosa and reduction of protective prostaglandins through the inhibition of COX-1. The risk of peptic ulcer varies according to duration of therapy, dosage of drugs, and type of NSAID. Weil et al reported that the OR for duodenal ulcer bleeding also increased with dosage of aspirin and other NSAIDs. Longer duration of therapy was also associated with increased risk of GI toxicity. Indomethacin, ketoprofen and piroxicam appear to be associated with the highest prevalence of GI toxicity, whereas ibuprofen and diclofenac appear to have lower rates.

Cardiovascular Toxicities: The New Concern of NSAIDs

The discovery of COX-2 provided the basis for the development of selective COX-2 inhibitors. COX-1 is a constitutively expressed enzyme which mediates the synthesis of thromboxane A2 in platelets and the production of protective prostaglandin of the gastric endothelium. COX-2 catalyzes prostaglandin synthesis in the inflammatory cells and leads to inflammation. Based on the hypothesis that anti-inflammatory effects are usually due to COX-2 inhibition and that adverse effects usually occur because of COX-1 inhibition, selective COX-2 inhibitors (celecoxib, rofecoxib, valdecoxib, etc.) were developed to reduce NSAID-associated GI toxicities. Several clinical trials showed a 41–57% reduction in the rate of GI toxicities with the use of selective COX-2 inhibitors. However, the VIGOR trial raised the issue of the cardiovascular safety of the coxibs after a statistically insignificant increase in the incidence of myocardial infarctions in patients on rofecoxib was found. The first well-known cardiovascular toxicities of coxibs arose from chemoprevention trials for colorectal polyps, when large doses and longer durations of treatment were needed. In the APPROVe trial, a significantly increased risk (relative risk, 1.97) of cardiovascular events as compared to placebo was shown. The results led to the withdrawal of rofecoxib in 2004. A meta-analysis including 17 case-controlled studies and six cohort studies revealed a dose-related cardiovascular risk for rofecoxib. The ORs for the cardiovascular risks of rofecoxib were 1.33 and 2.19 for dosages of ≤25 mg/day and >25 mg/day, respectively. Celecoxib at the usual doses was not associated with an elevated risk of vascular occlusion, with a relative risk of 1.06 (95% confidence interval [CI], 0.91–1.23). This meta-analysis also raised serious questions about the increased cardiovascular risks of diclofenac, with a relative risk of 1.40 (95% CI, 1.16–1.70). Naproxen was not associated with an increased risk of cardiovascular events, with a relative risk of 0.97 (95% CI, 0.87–1.07). Taken together, the cardiovascular toxicities seem to vary depending on type, dosage and duration of NSAID treatment. Intriguingly, geographic or ethnic differences may also play a role. A recent population-based analysis in Taiwanese adults with long-term (≥180 days) use of NSAIDs reported that no significant differences in the risk of treatment-related cardiovascular events were observed between groups treated with nonselective NSAIDS (etodolac, nabumetone, ibuprofen, naproxene) or celecoxib.
Gastroprotective Strategies for NSAID users

Owing to the potential serious GI complications associated with nonselective NSAIDs, several strategies have been used to decrease the risks, including: (1) use of selective COX-2 inhibitors; (2) eradication of *H. pylori* infection; and (3) co-prescription of gastroprotective agents. Selective COX-2 inhibitors are indeed effective for reducing GI adverse events, but their cardiovascular toxicities might restrict their utilization, especially when large-dose and long-term use are required. The other two strategies deserve further discussion.

**Eradication of *H. pylori***

In a meta-analysis of 25 observational studies (8843 patients), Huang et al found that *H. pylori* infection and NSAIDs increase the risk of peptic ulcers independently and have synergistic effects. Compared with *H. pylori*-negative individuals not taking NSAIDs, the ORs of ulcer were 18.1 for *H. pylori*-positive non-NSAID users, 19.4 for *H. pylori*-negative NSAID users, and 61.1 for *H. pylori*-positive NSAID users. Another meta-analysis by Vergara and colleagues found that the incidence of peptic ulcer in the overall population receiving NSAIDs was reduced after *H. pylori* eradication (7.4%), as compared to the control group (13.3%). Sub-analyses further showed a significant reduction in the risk of ulcer for non-NSAID users (OR, 0.26) but not for NSAID users (OR, 0.95).

**Co-prescription of gastroprotective agents***

The commonly used gastroprotective agents include misoprostol, H2-blocker, and proton pump inhibitors (PPI). Prophylactic use of antacids will not only not reduce the risk of GI toxicities, but may even mask the symptoms of subsequent serious GI complications such as bleeding. Misoprostol is a synthetic prostaglandin E1 analog used in the prevention of NSAID-induced peptic ulcers. A double-blind randomized controlled trial in 8843 patients with rheumatoid arthritis who were taking various NSAIDs showed that serious upper GI complications were reduced by 40% among patients who received misoprostol compared to those who received placebo (OR, 0.6; 95% CI, 0.364–0.982). However, misoprostol was poorly tolerated because of diarrhea and related problems. H2-blockers have also been used to prevent NSAID-related ulcers. However, a randomized controlled trial revealed that omeprazole healed and prevented ulcers more effectively than did ranitidine.

**Which strategy would be better in the prevention of GI toxicity?***

In very high risk patients (e.g. previous ulcer bleeding induced by nonselective NSAIDs), the most effective prevention strategy would be combination therapy. Chan et al found that celecoxib plus esomeprazole was better than celecoxib alone for the prevention of recurrent ulcer bleeding and could reduce the recurrent bleeding rate to 0%. A recent population-based, matched case-control analysis consisting of 1382 NSAID/COX-2 users with upper GI complications and 33,957 controls compared the effects of different strategies. The results demonstrated that all of the commonly accepted gastroprotective strategies (PPI, COX-2 inhibitors, low-dose/high-dose misoprostol), either alone or in combination, can reduce the risk of upper GI complications in NSAID users. This study also confirmed that the combination of COX-2 inhibitors with PPIs offers the greatest risk reduction. However, it was shown that celecoxib may be superior to the combination of nonselective NSAIDs with a PPI. In contrast to this study, Chan et al found that celecoxib was as effective as diclofenac plus omeprazole in patients with a recent history of ulcer bleeding. The probability of recurrent bleeding was 4.9% in the celecoxib group and 6.4% in the diclofenac plus omeprazole group during the 6-month period. Another important question is: would clopidogrel be better than PPI plus low-dose aspirin in preventing recurrent bleeding? Chan et al reported that the cumulative incidence of recurrent bleeding was 8.6% in the group treated with clopidogrel and
0.7% in the group treated with aspirin plus esomeprazole during the 12-month period; they concluded that the latter strategy is better.30

Next, is co-prescription of PPI or H. pylori eradication more effective in the prevention of recurrent upper GI bleeding? Chan et al found that for H. pylori-infected low-dose aspirin users, eradication therapy is equivalent to co-prescription of PPI in the prevention of recurrent upper GI bleeding.31 However, for other NSAID users who were H. pylori-infected, co-prescription of PPI is more effective than eradication therapy in the prevention of recurrent bleeding.31 A meta-analysis including two randomized controlled trials also revealed that co-prescription of PPI might be more effective (0%) than H. pylori eradication (2.6%) in the prevention of recurrent ulcer bleeding.24 However, whether co-prescription of PPI plus H. pylori eradication would be better than co-prescription of PPI alone in the primary prophylaxis of ulcer bleeding remains unknown.

**Strategies for choosing appropriate NSAID according to cardiovascular and GI risks**

It is recommended that a patient’s cardiovascular and GI risks be evaluated before the prescription of NSAIDs.1,32 Risk factors for the development of serious NSAID-related GI events include old age (> 60–65 years), history of peptic ulcer disease, H. pylori infection, higher dose or longer duration of NSAID use, when in the first few months of NSAID use, concomitant use of anticoagulants and corticosteroids, and other debilitating diseases.10–18 Cardiovascular risk may be assessed by the Framingham risk-score calculator, which estimates a patient’s 10-year risk of developing myocardial infarction and coronary death. The patient’s age, sex, smoking status, total and high-density lipoprotein cholesterol levels, systolic blood pressure, and whether or not the patient is on antihypertensive treatment are considered in the score.1,32

The general principles are that COX-2 inhibitor is preferred for patients with high GI risk, whereas naproxen is preferred for patients with high cardiovascular risk. Gastroprotective agents are recommended for patients receiving naproxen or with high GI risk. The recommended strategies according to cardiovascular and GI risks are shown in the Table.1,32 For patients with low cardiovascular risk, the choices of NSAIDs and gastroprotective agents can be managed according to their GI risk. Patients with low GI risk (without GI risk factors as described above) can be treated with nonselective NSAIDs alone. For patients with medium GI risk, either COX-2 inhibitor alone or nonselective NSAID plus a PPI or misoprostol is appropriate. For patients with high GI risk, COX-2 inhibitor plus a PPI or misoprostol is recommended. Among patients with high cardiovascular

<table>
<thead>
<tr>
<th>CV risk</th>
<th>GI risk</th>
<th>NSAIDs</th>
<th>Gastroprotective agent</th>
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<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>Nonselective</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>Nonselective</td>
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<tr>
<td></td>
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<td>COX-2 inhibitor</td>
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<td></td>
<td>Low</td>
<td>Naproxen</td>
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<td></td>
<td>Low-dose COX-2 inhibitor</td>
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<td></td>
<td>Medium</td>
<td>Naproxen</td>
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<td></td>
<td>High</td>
<td>Avoid NSAIDs if possible</td>
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<td></td>
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<td>Naproxen (if CV risk &gt; GI risk)</td>
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<td></td>
<td></td>
<td>Low-dose COX-2 (if GI risk &gt; CV risk)</td>
<td>+</td>
</tr>
</tbody>
</table>

NSAIDs = nonsteroidal anti-inflammatory drugs; CV = cardiovascular; GI = gastrointestinal; COX-2 = cyclooxygenase-2.
risk, naproxen plus a PPI or misoprostol are preferred if they have low/medium GI risk. Low-dose COX-2 inhibitor alone is also acceptable for patients with low GI risk. For patients with high cardiovascular risk and high GI risk, it is recommended that NSAIDs and COX-2 inhibitors be avoided if possible. If anti-inflammatory therapy is necessary, the choice of NSAID should be based on the relative importance of the GI and cardiovascular risks of an individual patient. There is currently no evidence to recommend which combination would be better for this group of patients, but co-prescription of a PPI or misoprostol is suggested. If the cardiovascular risk outweighs the GI risk, then naproxen is preferred over low-dose COX-2 inhibitor and vice versa. Randomized controlled trials are warranted to test the safety and efficacy of these recommendations for patients with high cardiovascular and high GI risks.

**Perspectives**

There remain some unresolved questions regarding the prevention of NSAID-related GI toxicities. First, whether or not routine screening for and treatment of *H. pylori* infection before the use of NSAID is effective in the primary prophylaxis of upper GI bleeding remains unknown because most of the previous studies used reduction in recurrent bleeding (secondary prophylaxis) as the end point. Second, whether or not the application of the recommended strategies as shown in the Table will reduce the occurrence (primary prophylaxis) of NSAID-related complications is also not known. Third, some host genetic factors (such as variant CYP2C9*3 allele) have been reported to increase host susceptibility to NSAID-related ulcer bleeding in Western populations.33,34 However, the variant CYP2C9*3 allele is very rare in Chinese populations.35 Further studies are warranted to identify the susceptible genes in Chinese populations. If such genes can be identified, personalized selection of NSAIDs and gastroprotective agents based on pharmacogenomic approaches might become feasible in the future.

**References**

14. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients...


