Review article: prevention of non-steroidal anti-inflammatory drug gastrointestinal complications – review and recommendations based on risk assessment

F. K. L. CHAN* & D. Y. GRAHAM†
*Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China; †Molecular Virology and Microbiology, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, TX, USA
Accepted for publication 4 March 2004

SUMMARY
The incidence of non-steroidal anti-inflammatory drug-related ulcer complications remains high despite the availability of potent anti-ulcer drugs and selective cyclo-oxygenase-2 inhibitors. Non-steroidal anti-inflammatory drug-related ulcer complications can be minimized by prospective assessment of patients’ baseline risk, rational choice and use of non-steroidal anti-inflammatory drugs, and selective use of co-therapy strategies with gastroprotectives. Current recommendations regarding strategies using anti-ulcer drugs and cyclo-oxygenase-2 inhibitors for prevention of clinical non-steroidal anti-inflammatory drug upper gastrointestinal events are largely derived from studies using surrogates such as endoscopic ulcers, erosions, and symptoms in low- to average-risk patients. Conclusions based on surrogate and potentially manipulatable end-points are increasingly suspect with regard to applicability to clinical situations. This article reviews the risks associated with non-steroidal anti-inflammatory drugs including aspirin and includes the effect of the patients’ baseline risk, and the confounding effects of Helicobacter pylori infection. In addition, uncertainties regarding the clinical efficacy of anti-ulcer drugs and cyclo-oxygenase-2 inhibitors against non-steroidal anti-inflammatory drug-related ulcer complications are put into perspective. We propose management strategies based on the risk category: low risk (absence of risk factors) (least ulcerogenic non-steroidal anti-inflammatory drug at lowest effective dose), moderate risk (one to two risk factors) (as above, plus an antisecretory agent or misoprostol or a cyclo-oxygenase-2 inhibitor), high risk (multiple risk factors or patients using concomitant low-dose aspirin, steroids, or anticoagulants) (cyclo-oxygenase-2 inhibitor alone with steroids, plus misoprostol with warfarin, or plus a proton pump inhibitors or misoprostol with aspirin), and very high risk (history of ulcer complications) (avoid all non-steroidal anti-inflammatory drugs, if possible or a cyclo-oxygenase-2 plus a proton pump inhibitors and/or misoprostol). The presence of H. pylori infection increases the risk of upper gastrointestinal complications in non-steroidal anti-inflammatory drug users by two- to fourfold suggesting that all patients requiring regular non-steroidal anti-inflammatory drug therapy be tested for H. pylori.

INTRODUCTION
Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs worldwide and are especially valued for their analgesic, antipyretic and anti-inflammatory properties. However, despite the great benefits associated with NSAID use, up to 25% of patients taking NSAIDs chronically experience upper gastrointestinal (UGI) adverse effects. There are several management principles and options that can reduce the risk of NSAID-induced complications including issues regarding dose, type of NSAID, and gastroprotective...
drug therapy consisting of either co-therapy with antisecretory drugs or 'prostaglandin replacement' with misoprostol. It has also been recently recognized that Helicobacter pylori-infected individuals have about a twofold increased risk of developing complications while taking aspirin or traditional NSAIDs making H. pylori eradication another option to reduce risk.\textsuperscript{2, 3} Case–control studies have consistently shown that NSAIDs differ in their ulcerogenic risk and this fact alone suggests that care in selection of an NSAID to match the indication should reduce the incidence of untoward events.\textsuperscript{4–7}

ASSessment of ulcer risk

The strongest risk factor for a GI complication is the presence of prior ulcer disease with a history of ulcer complications.\textsuperscript{8} Other important risk factors include old age, presence of cardiovascular diseases, concomitant use of aspirin or other antiplatelet drugs, steroids or warfarin. In clinical practice, patients can be stratified into three groups of progressive risk and a fourth group of very high-risk patients (i.e. the presence of prior ulcer complications). The three primary risk groups can be separated according to the number and nature of risk factors: low risk (absence of risk factors), moderate risk (one to two risk factors), and high risk (≥3 risk factors, or concomitant use of aspirin). According to the MUCOSA study, the estimated annualized incidence of NSAID-related ulcer complications was 0.8% for patients without risk factors, 2% with one risk factor, 7.6–8.6% with three risk factors and 18% with four risk factors.\textsuperscript{9}

choosing the right NSAID for the right patient

The best and cheapest method to prevent an NSAID-related ulcer complication is to avoid NSAID use. Non-NSAID analgesics should be the first line treatment for patients with degenerative arthritis or other non-inflammatory pain conditions. If NSAIDs are required, the important issues are related to cost, safety and effectiveness. Recently, a nomogram has been developed that incorporates factors including patients' baseline risk, the added risk associated with the individual NSAID, and the cost of and protection conferred by co-therapy to estimate the cost-effectiveness of competing strategies for reducing the risk of clinical UGI events.\textsuperscript{10} The nomogram is useful to rapidly calculate relative cost-effectiveness of the various trade-offs (Figure 1).

In general, the GI toxicity of a cyclo-oxygenase (COX) non-selective NSAID correlates with its anti-inflammatory activity. NSAIDs with a high analgesic effect at

<table>
<thead>
<tr>
<th>(a) Cost Difference $/year</th>
<th>(b) UGI Event Difference %/year</th>
<th>(c) Additional Cost Per UGI Event Prevented ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1500</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>800</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>.8%</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>.5%</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>.3%</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>.1%</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. The Figure represents nomogram designed to estimate the cost-effectiveness of competing strategies for reducing the risk of clinical upper gastrointestinal (GI) events. (a) Denotes the difference in the annual cost between any two strategies of non-steroidal anti-inflammatory drug (NSAID) use; (b) denotes the difference in the annual rate of clinical upper GI events; (c) denotes the incremental cost-effectiveness ratio, which is the additional cost per clinical upper GI event prevented. Strategies with smaller incremental ratios are more cost-effective (reproduced with permission).\textsuperscript{10}
doses with low anti-inflammatory activity, such as ibuprofen, are less ulcerogenic than NSAIDs that achieve adequate analgesic effect only at doses with high anti-inflammatory activity (e.g. piroxicam).\textsuperscript{11} Ibuprofen appears safe among other non-selective NSAIDs in part because it is frequently prescribed for temporary painful conditions thus limiting both duration and dose.\textsuperscript{12} However, when full anti-inflammatory doses are given (e.g. 2.4 g/day), the risk of GI bleeding with ibuprofen is comparable with other NSAIDs.\textsuperscript{13} For pain relief, we recommend an NSAID with a high analgesic effect and low anti-inflammatory action (e.g. ibuprofen) and the lowest effective dose should be used. Selective cyclo-oxygenase-2 (COX-2) inhibitors provide good analgesia with increased safety but at greater expense. For a temporary problem (e.g. toothache or headache) it is unlikely that the expense of COX-2 selective drugs justifies it use in terms of the safety benefit. For patients who require NSAIDs for inflammatory conditions, NSAIDs with short half-lives (e.g. indometacin) provide good control of acute arthritis (e.g. gout) whereas NSAIDs with longer half-lives (e.g. naproxen) are preferred for chronic conditions (e.g. rheumatoid arthritis). If all things including costs were equal, we would only prescribe selective COX-2 inhibitors for any indication where an NSAID is needed.

**GASTROPROTECTIVE THERAPY**

Studies evaluating different strategies to prevent NSAID-induced ulcers with antisecretory drugs, misoprostol, or other agents have used ‘endoscopic’ ulcers as surrogates for clinical ulcer disease or for clinical events such as bleeding or perforation. Initially, an endoscopic ulcer was arbitrarily defined as a circumscribed mucosal break with a diameter of at least 5 mm and a perceptible depth.\textsuperscript{14} The 5 mm definition with apparent depth definition was chosen to try to minimize confusion with NSAID erosions. The definition of 3 mm diameter ‘ulcer’ was introduced as part of the strategy to obtain Food and Drug Administration (FDA) approval for a low dose (800 mg) of cimetidine for use in healing of *H. pylori* duodenal ulcers. Approval of that dose of cimetidine with apparent depth definition was chosen to try to minimize confusion with NSAID erosions. The definition of 3 mm diameter ‘ulcer’ was introduced as part of the strategy to obtain Food and Drug Administration (FDA) approval for a low dose (800 mg) of cimetidine for use in healing of *H. pylori* duodenal ulcers. Approval of that dose of cimetidine with that definition resulted in it becoming the new FDA criteria for ulcers.\textsuperscript{15} However, endoscopists often may have difficulty in distinguishing between the presence of NSAID-induced discrete acute mucosal lesions that come and go rapidly and have no known correlation to chronic ulcers or clinical events and a clinically significant NSAID ulcer. Most recent studies of NSAID ulcer prevention have used the definition of an endoscopic ulcer as any lesion 3 mm or greater in diameter with or without apparent depth. The significance of such trivial lesion is uncertain and ulcers are over diagnosed. For example, a blinded review of the teaching tape for investigators participating in NSAID ulcer prevention trials showed that a high proportion of lesions scored as ‘ulcers’ would not be scored as ulcers by experienced endoscopists.\textsuperscript{16} Below we discuss the potential impacts of the use of endoscopic ulcers, erosions, and symptoms as end-points, either individually or as a composite score.

**H\textsubscript{2}-receptor antagonists**

In a pooled analysis of five randomized-controlled trials of H\textsubscript{2}-receptor antagonists for the prevention of gastro-duodenal ulcers associated with NSAID use, it was found that standard doses of H\textsubscript{2}-receptor antagonists reduced the risk of duodenal but not gastric ulcers.\textsuperscript{17} Data from three randomized trials suggested that double-dose H\textsubscript{2}-receptor antagonists are effective against NSAID-related duodenal and gastric ulcers although the majority of the effect was among those with a history of prior ulcers.\textsuperscript{18-20} One study in the USA used a protocol identical to the European trial and failed to show a statistical benefit. It was only published as an abstract (possibly publication bias).\textsuperscript{21} The reported efficacy of double-dose H\textsubscript{2}-receptor antagonists has also varied among the studies. In one study,\textsuperscript{18} those whose ulcers were healed at 12 weeks were continued in a 24-week maintenance trial comparing famotidine and placebo. The rates of gastric ulcers at 24 weeks were 26% (52 per 100 patient years) and 53.5% (107 per 100 patient years) in the groups receiving double-dose famotidine and placebo, respectively. Post hoc subgroup analysis showed that the effect was essentially limited to those with *H. pylori* infection as the recurrence rate among those without *H. pylori* infection was 23.8% with placebo compared with 21.4% for those receiving famotidine.\textsuperscript{15} Overall, the data suggested that the major benefit from H\textsubscript{2}-receptor antagonists might be limited to those with *H. pylori* infection and provided important information regarding critical subgrouping that should have been taken into account when designing the subsequent proton pump inhibitor (PPI) ulcer prevention trials.
**Proton Pump Inhibitors**

The potential role of PPIs for prevention of NSAID-induced gastroduodenal damage has been evaluated in a number of large-scale, drug company sponsored, multicentred studies. None of these trials used clinical events as end-points and all used surrogate end-points often as composite end-points that included endoscopic ulcers, erosions and symptoms. The tremendous difference in antisecretory activity of the comparators (half dose misoprostol or standard dose ranitidine) essentially ensured that if acid sensitive symptoms were present [i.e. gastro-oesophageal reflux disease (GERD) or GERD-like] that the PPI would appear superior. Two placebo-controlled endoscopic studies assessed the efficacy of omeprazole for the prevention of gastroduodenal ulcers associated with NSAIDs.\(^{22, 23}\) The reported incidences of ulcer ranged from 7.2 to 18.8 per 100 patient years in the omeprazole group compared with 33–66.8 per 100 patient years in the placebo group. Importantly, the proportion developing ulcers among those without \(H.\ pylori\) infection and no history of ulcer disease was 3% among omeprazole user compared with 2.6% among those receiving placebo.

In the ASTRONAUT study\(^{24}\) and the OMNIUM study,\(^{25}\) omeprazole was compared with standard dose ranitidine (150 mg b.d.) (which parenthetically had repeatedly been shown to be ineffective for NSAID ulcer prevention\(^{26}\)) and to half dose misoprostol (200 \(\mu g\) b.d.) (equivalent to approximately 600 mg of cimetidine as an antisecretory drug) over a period of 24 weeks. The definition of an ulcer was a lesion >3 mm diameter. The primary end-point was a composite of endoscopic ulcers, multiple erosions and severe dyspepsia (mostly heartburn where the PPI was likely to be superior to either misoprostol or standard dose ranitidine). The investigators did not report detailed results with \(H.\ pylori\)-positive and -negative separately despite the evidence from the \(H_2\)-receptor antagonist trials that was likely to be critical.\(^{15}\) In the ASTRONAUT study,\(^{24}\) 28% (56 per 100 patient years) of patients in the omeprazole group compared with 41% (82 per 100 patient years) of patients in the ranitidine group had treatment failure. Post hoc subgroup analyses of the development of ulcer among those with and without \(H.\ pylori\) infection showed that the majority of the advantage among omeprazole users was in the \(H.\ pylori\) infected patients.\(^{27}\) In fact, half dose misoprostol proved significantly superior to omeprazole for both healing of gastric ulcers and prevention of gastric ulcers among those without \(H.\ pylori\) infection.\(^{27}\) There was a significant advantage for omeprazole over standard dose ranitidine among those with \(H.\ pylori\) infection but no statistical advantage among the \(H.\ pylori\)-negative patients. The advantage of omeprazole vs. ranitidine for prevention of gastric ulcer was 10.5% vs. 14.6% (21 vs. 30 per 100 patient years) and for duodenal ulcer was 1.2% vs. 2.1% (2.4 vs. 4.2 per 100 patient years).\(^{27}\)

Based on the data from the \(H.\ pylori\)-negative patients, the sample size to show a statistical advantage for the PPI over standard dose ranitidine would require more than 1800 patients for an outcome of both duodenal ulcer (DU) and gastric ulcer (GU), and more than 2200 for the outcome of GU alone. Planning head-to-head studies with fewer patients would likely risk failure to achieve a statistical advantage. The only potential advantage of \(H_2\)-receptor antagonists has been cost. Whether these small differences are clinically important are another matter but the marked reduction in price for PPI expected now that the patent for omeprazole has expired may make cost differences moot.

**Misoprostol**

A meta-analysis of 33 randomized-controlled clinical trials of misoprostol, \(H_2\)-receptor antagonists and PPIs revealed that all three classes of drugs reduce the incidence of NSAIDs-related gastroduodenal ulcers.\(^{17}\) Only standard dose misoprostol (200 \(\mu g\) q.d.s.) has been tested for its ability to reduce NSAID-related ulcer complications\(^{9}\) and it proved partially effective (approximately 40% reduction). However, side-effects such as abdominal cramps and diarrhoea were common such that the median dose in that study was only about 600 \(\mu g\). Misoprostol provides ‘physiologic replacement therapy’ and its effects extend beyond the stomach. Thus, it is theoretically better than therapy aimed at only reducing acid secretion. The fact that NSAIDs can produce ulcers and ulcer complications in patients with achlorhydria is rarely discussed but suggests that prostaglandin replacement therapy would be ideal approach if it could be offered in a way to minimize side-effects.\(^{28}\) The effectiveness of misoprostol over standard and double doses of PPIs has been confirmed in a study\(^{29}\) of standard dose misoprostol (200 \(\mu g\) q.d.s.) with two doses of lansoprazole (15 and 30 mg daily) among \(H.\ pylori\)-negative chronic NSAID users who had a history of gastric ulcer. Misoprostol proved superior.
for prevention of gastroduodenal ulcer. For example, at 12 weeks, 93% of patients in the misoprostol group compared with 80–82% of patients in the two groups receiving lansoprazole were protected from gastric ulcers. The ulcer rates were 15, 43, 47 per 100 patient years, for misoprostol, lansoprazole 15 mg, and 30 mg, respectively. However, because of the higher withdrawal rate in the misoprostol group, there was no practical advantage of misoprostol over lansoprazole. However, it is impossible to prospectively identify those who will experience symptoms from misoprostol making a clinical trial the only practical method of identifying those in whom it might be the preferred drug. Because misoprostol and antisecretory agents act via different mechanisms, it is possible that the combination of half dose misoprostol and an H₂-receptor antagonist or a PPI (e.g. generic omeprazole) would provide inexpensive yet effective preventive therapy for high-risk patients. The fact that the majority of patients took misoprostol without problems in the large clinical trials suggests that individual patients and not physicians should decide whether it can be used successfully.

**COX-2 INHIBITORS**

The discovery of a second isoform of COX-2 led to the rapid development and marketing of highly selective COX-2 inhibitors as gastric sparing anti-inflammatory analgesics and anti-inflammatory agents. There is good evidence that this new class of NSAIDs causes minimal endoscopic gastric damage. The extent to which these endoscopic findings translate into clinical benefits remains unclear. Two large-scale clinical outcome studies, CLASS and VIGOR, attempted to evaluate the GI safety of celecoxib and rofecoxib, respectively. The CLASS study was initially designed as a 12-month study of celecoxib vs. diclofenac or ibuprofen. Analysis of the first 6 months data showed that celecoxib was superior to non-selective NSAIDs among patients who did not receive concomitant low-dose aspirin. However, the long-term outcome of CLASS subsequently presented at the US FDA hearings failed to confirm a significant advantage of celecoxib over the comparators. Whether the failure of CLASS was due to flaws in the study design (for example, preferential dropout of patients receiving non-selective NSAIDs), some ulcerogenicity of celecoxib, or inclusion of patients with *H. pylori* ulcers or ulcer complications, remains uncertain. Unlike CLASS, VIGOR showed that patients receiving rofecoxib had a significantly lower incidence of clinical UGI events compared with patients receiving naproxen. However, ‘significantly lower’ did not approximate the desired ‘none’. In the VIGOR study, patients requiring low-dose aspirin were excluded. This was in marked contrast to the CLASS study where 20% of patients received concomitant low-dose aspirin. Given the low incidence of events in these studies, the fact that a 1–2% incidence of events was to be expected among aspirin users, and that patients with prior *H. pylori* ulcers were entered, it is not surprising that there was difficulty showing superiority over any comparator. Part of the reason for ‘poor designs’ was related to the pharmaceutical company not wanting a restricted claim (e.g. patients with no history of *H. pylori* ulcers, ulcer complications, not taking aspirin). Post hoc subgroup analysis showed that patients with prior UGI events did not have a significant reduction in the incidence of new ulcer complications despite use of the COX-2 inhibitor, rofecoxib, instead of naproxen. This result is consistent with the fact that patients with prior ulcer complications either caused by *H. pylori* or NSAIDs represent a special high-risk group (e.g. the one where one would most prefer to use selective COX-2 inhibitors). The fact that these patients represent a special group was emphasized by a recent randomized, GI outcome study of celecoxib vs. omeprazole plus diclofenac in patients with a recent history of ulcer bleeding. The 4.9% (9.8 per 100 patient years) of patients in the celecoxib group compared with 6.4% (12.8 per 100 patient years) in the omeprazole plus diclofenac group had recurrent ulcer bleeding. Although the two treatments were comparable, the study could not address whether either was superior to placebo and neither strategy was sufficiently effective to be recommended for these very high-risk patients. In addition, up to 30% of these high-risk patients developed renal adverse events including hypertension, fluid retention and renal failure with either treatment. There was also one small bowel perforation resulting in a death in the omeprazole plus diclofenac group.

**ROLE OF HELICOBACTER PYLORI INFECTION**

There are studies reporting that *H. pylori* infection increases, has no effect on, or even decreases the risk of NSAID-related ulcers. One reason for these conflicting findings is fact that the studies have rarely taken the natural history of *H. pylori* infection into account nor
have the pre-existing risks been considered, stratified for, or specifically acknowledged. The risk for developing an ulcer among those with latent *H. pylori* infection is approximately 1% per year (1 per 100 patient years) independent of NSAID use. The risk of a GI complication among those with *H. pylori* ulcers who have never experienced a complication is also in the range of 1 per 100 patient years. Therefore, the risk for a new *H. pylori* ulcer complication among those with latent *H. pylori* infection is <1 per 1000 patient years and would remain invisible in most clinical trials. In marked contrast, 50–100% of those with a history of *H. pylori*-related ulcer will develop a recurrent ulcer within any 1 year (especially if evaluated by endoscopy) irrespective of NSAID use. NSAID users who had prior *H. pylori* ulcer disease would therefore be expected to develop ulcers during follow-up and, as it would be impossible to distinguish whether the ulcer was related to the NSAID use, the *H. pylori* infection, or to an interaction, entry of such patients only serve to bias the outcome. Ulcer complications among those with *H. pylori* ulcers are expected in 1–2% per year. Thus, inclusion of *H. pylori* ulcer patients would result in an increase in the number of new complications unrelated to NSAID use and provide another source of major bias. Thus, inclusion of patients with prior *H. pylori* ulcers can only serve as a source of potential bias that can also markedly and potentially erroneously influence the results (see later). Any *H. pylori*–NSAID interaction would also accentuate the number of events and complicate the interpretations.

Patients at highest risk of developing an ulcer complication are those who have experienced an ulcer complication in the past. The risk of a new ulcer complication after one complication in *H. pylori* ulcers is in the range of 1–3% per month (12–36 per 100 patient years) even without exposure to NSAIDs. Therefore, such patients must be excluded unless this issue is being specifically studied. The inclusion of these patients has resulted in them being repeatedly identified as the group at highest risk, which was neither useful nor new information in relation to NSAID risk. Importantly, their inclusion will predictably bias the outcome and can easily lead to misleading conclusions regarding the safety of a particular compound, the effectiveness of the gastroprotective therapy, or conversely, the comparative value of different therapies.

The issue is further complicated as data suggest that patients with *H. pylori* infection who start NSAIDs are at a higher risk of ulcer than *H. pylori*-infected patients who are already on long-term NSAIDs. Eradication of *H. pylori* before starting NSAIDs has been shown to reduce the subsequent risk of ulcer (e.g. in one study from 26% to 7% over a period of 8 weeks). Among patients with *H. pylori* infection who were already on long-term NSAIDs, however, curing the infection was not effective for prevention of NSAID ulcers possibly because a prior bad experiences with NSAIDs may have served to identify those at special risk (e.g. those with latent *H. pylori* ulcers) and to have eliminated them. Eradication of *H. pylori* is not expected to greatly affect recurrence of NSAID ulcers among NSAID users. For example, the first studies of anti-*H. pylori* therapy showed that ulcer recurrence was eliminated by *H. pylori* eradication except in those where there was failure to cure the infection or where there was use of NSAIDs. Thus, it is not surprising that eradication of *H. pylori* among chronic NSAID users would not affect the incidence of NSAID ulcers among those free of ulcer at the start of a clinical trial.

**ASPIRIN, AN NSAID WITH SPECIAL PROBLEMS**

Aspirin has been increasingly used for prevention of cardiovascular events and is now probably the most commonly used NSAID. An estimated of 50 million Americans have started taking aspirin over the past two decades. The decision regarding whether the risks of GI haemorrhage with aspirin are clinically acceptable depends on an estimation of the expected benefits compared with the risks of vascular events. In a meta-analysis of the risk of GI bleeding (severity undefined) with long-term use of low-dose aspirin, it was estimated that about one in 248 subjects would develop GI bleeding with aspirin per year. In the secondary prevention of stroke, the number needed to treat with aspirin to prevent a further cardiovascular event was only 106 which means that more than two recurrent strokes could be prevented with aspirin at the cost of one GI bleed. By contrast, the number needed to treat for the primary prevention of myocardial infarction per year ranged from 555 in the US Physicians Health Study to 794 in hypertensive patients. Thus, in patients at low risk for cardiovascular events, aspirin use could cause five to seven GI bleeds for each episode of myocardial infarction prevented. The US Food and Drug Administration recently reviewed aspirin for primary prevention and
declined to approve it. There was a significant (approximately 25%) reduction in non-fatal myocardial infarction, no reduction in deaths and a slight increase in haemorrhagic stroke. This contrasts with secondary prevention where strokes, deaths, and myocardial infarctions were all reduced. No dose of aspirin is free of bleeding risk. Even at a dose as low as 75 mg/day, the risk of UGI bleeding is two times higher than among non-users. Recent post hoc analysis of observational studies examined the effect after grouping doses as ≥200, >101–199 and <100 mg/day among 12 562 aspirin users randomized to receive clopidogrel or placebo in the treatment of acute coronary syndrome. Although, the study was post hoc and observational, the data were internally consistent suggesting that the lowest dose was safer than high doses; 75–81 mg are recommended.

Long-term prevention trials with highly selected patients have reported severe bleeding or death to be in the range of 0.1–0.3 per 100 patient years. This appears to be about 10-fold less than ‘any bleeding’. In contrast, the risk of a potentially life-threatening bleeding event in the CURE study mentioned above was considerably greater (1.9 per 100 patient years with <100 mg to 3.9 per 100 patient years in those receiving 200–365 mg of aspirin). These are at least 10-fold greater than seen in the long-term aspirin prevention trials and are more consistent with use in clinical practice. One should probably expect somewhere between the two extremes probably closer to 1% (1 per 100 patient years than to 0.3 per 100 patient years). Because of its widespread use and its effect on platelets, aspirin use must be considered separately when planning prevention strategies (Table 1).

### STRATEGIES FOR PREVENTION OF NSAID-RELATED ULCER COMPLICATIONS

#### Management of low-risk patients

Patients without risk factors are at low, but not insignificant, risk of ulcer complications with NSAID use. Because of the vast number of consumers, this group constitutes the majority of cases of NSAID-associated ulcer complications each year. The most cost-effective approach for prevention of ulcer complications in this low-risk category is rational use of NSAIDs. As mentioned earlier, a substantial proportion of cases of ulcer complications could be avoided by using simple analgesics or NSAIDs with low ulcerogenic potentials, avoiding high dose or multiple (prescription and non-prescription) NSAIDs. COX-2 inhibitors are safer than the least ulcerogenic conventional NSAIDs such as ibuprofen and diclofenac. However, the high cost of COX-2 inhibitors renders these drugs not cost-effective especially for short-term treatment of low-risk individuals.

#### Management of moderate-risk patients

This category consists of patients with one or two risk factors who are often elderly. We recommend the combination of a non-selective NSAID and misoprostol.

<table>
<thead>
<tr>
<th>Group</th>
<th>Strategies recommended by authors</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk (no risk factors)</td>
<td>Least ulcerogenic NSAIDs at lowest effective doses</td>
<td>PPI is preferred to H2-receptor antagonist</td>
</tr>
<tr>
<td>Moderate-risk (one to two risk factors)*</td>
<td>Least ulcerogenic NSAID plus an antisecretory agent or misoprostol COX-2 inhibitor</td>
<td>Misoprostol 200 μg t.i.s. is recommended</td>
</tr>
<tr>
<td>High-risk (≥3 risk factors or concomitant aspirin, steroids, or warfarin)</td>
<td>COX-2 inhibitor plus PPI or misoprostol for concomitant aspirin COX-2 inhibitor plus misoprostol for concomitant warfarin COX-2 inhibitor for concomitant steroids</td>
<td>Recommendations are based on post hoc subgroup analysis and preliminary data only</td>
</tr>
<tr>
<td>Very high-risk patients (history of recent ulcer complications)</td>
<td>Avoid NSAIDs all together COX-2 inhibitor plus PPI and/or misoprostol</td>
<td>Avoiding NSAIDs is the best approach Recommendation not tested clinically</td>
</tr>
</tbody>
</table>

* Old age, presence of cardiovascular diseases, use of high dose or multiple NSAIDs, concomitant use of low-dose aspirin and other antiplatelet drugs, steroids or warfarin.

NSAID, non-setroidal anti-inflammatory drug; COX-2, cyclo-oxygenase-2; PPI, proton pump inhibitors.

or an antisecretory agent. Alternatively, substitution for a COX-2 inhibitor alone is probably as effective as the combination therapy. The former has the advantage of taking fewer tablets. Emerging data suggest that treatment with a COX-2 inhibitor causes less lower GI complications than treatment with an NSAID plus an antisecretory agent. The magnitude of this problem is unclear and likely to be quite low. Whether it will eventually turn out to be more than a marketing point used to help differentiate drug remains uncertain.

**Management of specific groups of high-risk patients**

This category consist of patients with multiple risk factors or patients using concomitant low-dose aspirin, steroids, or anticoagulants. In general, NSAIDs should be avoided in these patients not only because of the high risk of ulcer complications but also due to the serious consequence of ulcer complications in the presence of comorbidities.

**Patients receiving concomitant aspirin.** Aspirin at any dose increases the risk of ulcer complications, which is further increased by the presence of an *H. pylori* infection. It is not clear whether low-dose aspirin adds significantly to the risk of chronic NSAID therapy with non-selective NSAIDs. In contrast, there are data suggesting that chronic NSAID use may reduce the effectiveness of aspirin for cardiovascular protection. The best data for an interaction comes from studies of interactions with ibuprofen. In addition, post hoc subgroup analyses of the Physicians Health Study suggested that chronic use of traditional NSAIDs was associated with a reduction in aspirin’s cardiovascular protective benefits. We anticipate many more studies where pharmaceutical companies test their individual NSAID for this interaction in that lack of an effect provides a marketing advantage. The selective COX-2 inhibitors do not have this interaction and are therefore preferred for those who need secondary cardiovascular prophylaxis with aspirin and an NSAID. Unfortunately, as aspirin carries its own risks for ulcer and ulcer complications, gastric damage may occur despite the gastric sparing effect of COX-2 inhibitors. The best course of action remains unclear and as always depends on an analysis of benefits, risks and costs.

For higher risk patients in whom a significant GI event would be expected to aggravate myocardial or cerebral ischaemia, we recommend the combination of a COX-2 inhibitor, low-dose aspirin (<100 mg) and a PPI or misoprostol if concomitant anti-inflammatory and antiplatelet therapies are both required. The recent introduction of generic omeprazole in the United States should result in costs becoming less of an issue. As noted above, co-therapy with misoprostol and aspirin looks very good in clinical trial but has not been evaluated in the setting where it would be of most benefit. Nitrous oxide donating aspirin (NO-aspirin) offers a theoretical advantage but has also not yet proven to be effective clinically. There is evidence that other antiplatelet agents such as ticlopidine or clopidogrel carry a higher risk of GI bleeding than aspirin at doses of <100 mg/day such that substitution of low-dose aspirin for other antiplatelet agents is not recommended.

**Patients receiving concomitant steroids or anticoagulants.** Few clinical conditions require concomitant use of steroids and NSAIDs since short-term steroid therapy or disease-modifying drugs can usually control inflammatory arthritis. Nonetheless, concomitant use of steroids and NSAIDs is not rare and often consists of self-medication with over-the-counter drugs containing aspirin or NSAIDs. Patients should be warned to avoid taking these drugs while taking prescription NSAIDs. Post hoc subgroup analysis of VIGOR suggested that concomitant steroid use did not increase the risk of clinical UGI events among patients receiving rofecoxib. While this result suggests that COX-2 inhibitors are a potential alternative to conventional NSAIDs along with an antisecretory drug or misoprostol for patients receiving concomitant steroid therapy, the results of post hoc subgroup analyses must always be confirmed in prospective randomized-controlled clinical trials.

It is prudent to always be somewhat wary regarding the conclusions of post hoc subgroup analyses ‘dredged’ from large pharmaceutical trials in part because of the stringent entry criteria usually selects good risk patients that are often markedly different from the high-risk populations in whom the physician needs help. In addition, because many post hoc subgroup analyses are undergone, the companies are assured of obtaining some with positive and some with negative results. Generally, only the associations that are positive for the drug being tested are reported and we are essentially never given the number of comparisons done to find the reported association. Negative associations are also
rarely reported robbing the physician of knowledge of subgroups where the new drug might not be the best choice.

Studies based on healthy volunteers suggested there is no clinically important interaction between COX-2 inhibitors and anticoagulants. Patients who receive anticoagulants usually have serious medical conditions such as prosthetic heart valve replacement or deep vein thrombosis, such that the consequences of GI bleeding or withholding anticoagulants is potentially disastrous and NSAIDs including COX-2 inhibitors should be avoided. In rare occasions that long-term anti-inflammatory therapy is required, we recommend the combination of a COX-2 inhibitor and misoprostol. Misoprostol is preferred to antisecretory drugs because anticoagulants can provoke bleeding from pre-existing ulcers along with the whole GI tract. Theoretically, the combination of a COX-2 inhibitor and misoprostol reduces the risk of both upper and lower GI bleeding.

**Management of very high-risk patients**

Patients with prior ulcer complications. As noted earlier, patients with a history of ulcer complications have the highest risk of recurrent ulcer bleeding. This also holds true for NSAID users. The outcome may depend in part on the cause of the ulcer disease and the time after ulcer healing and, in those with *H. pylori* infection, the duration since *H. pylori* eradication. In one study, about 19% (38 per 100 patient years) of NSAID users with *H. pylori* infection and a recent history of ulcer bleeding developed recurrent bleeding with naproxen in 6 months after eradication of *H. pylori*, which is within the 12–36% range expected from prior studies with *H. pylori* ulcers. Current strategies for prevention of ulcer complications in these high-risk NSAID users include substitution of COX-2 inhibitors for non-selective NSAIDs and co-therapy of NSAIDs with a PPI, misoprostol, or both. As noted earlier, when these empiric recommendations were subjected to a randomized, head-to-head comparison of celecoxib vs. diclofen-ac plus omeprazole, neither strategy proved effective for eliminating the risk of recurrent bleeding in patients prior ulcer bleeding. In that study the estimated annualized incidence of recurrent bleeding was about 10%. That study emphasized that the current recommendations were not based on evidence but were based on the surrogate end-points from the endoscopic ulcer trials. The conclusion of trials using surrogate and end-points that potentially can be easily manipulated end-points are increasingly suspect with regard to applicability to clinical situations. We conclude that very high-risk patients should avoid NSAIDs. If short-term anti-inflammatory therapy is required for acute, self-limiting arthritis (e.g. gout), we recommend the use of steroids, since steroids alone do not increase the ulcer risk. If regular anti-inflammatory therapy is required for chronic arthritis, the combination of a COX-2 inhibitor and misoprostol and possibly a PPI probably offers the best GI protection although this approach remains to be examined in prospective trials.

**CONCLUSION**

Ironically, despite the availability of potent anti-ulcer drugs and new developments in anti-inflammatory therapies, the incidence of NSAID-related morbidity and mortality remains high. Failure to take into account risk factors, inappropriate use of NSAIDs, and lack of anti-ulcer prophylaxis in high-risk patients account for a substantial proportion of preventable NSAID-related ulcer complications. The importance of education for primary care doctors and patients cannot be over-emphasized.

Contrary to the findings in low- to average-risk individuals, current evidence suggests that neither co-therapy with an anti-ulcer drug or substitution of a COX-2 inhibitor for a traditional NSAID is a safe strategy for management of very high-risk patients or those with multiple-risk factors. Studies are needed to evaluate the gastric safety of anti-ulcer drugs and COX-2 inhibitors in different risk groups using clinical outcomes rather than endoscopic mucosal injury as end-point. Since *H. pylori* significantly augments the efficacy of PPIs, the true efficacy of PPIs for prevention of NSAID-related ulcer complications must be reassessed without the confounding influence of *H. pylori*.

**ACKNOWLEDGMENTS AND POTENTIAL CONFLICTS OF INTEREST**

This material is based upon work supported in part by the Office of Research and Development Medical Research Service, Department of Veterans Affairs and by Public Health Service grant DK56338, which funds the Texas Gulf Coast Digestive Diseases Center. In the last 3 years, Dr Graham has received research support or honoraria for speaking engagements from AstraZen-
REFERENCES


16 Sung JY, Lau JY, Chan FK, Graham DY. How often are endoscopic ulcers in NSAID trials diagnosed as actual ulcers by experienced endoscopists [Abstract]. Gastroenterology 2001; 120(Suppl. 1): A597.


29 Graham DY, Agrawal NM, Campbell DR, et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory
randomized, controlled study of misoprostol vs. lan-