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Management of NSAID-Induced Gastrointestinal Toxicity

Focus on Proton Pump Inhibitors

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Contents

Abstract

The association between NSAIDs and the presence of upper gastrointestinal (GI) complications is well established. Evidence that acid aggravates NSAID-induced injury provides a rationale for minimizing such damage by acid suppression.

Proton pump inhibitors (PPIs) appear to be very effective in treating NSAID-related dyspepsia, and also in healing gastric and duodenal ulcers in patients continuing to receive the NSAID. An analysis of data from comparative studies of PPIs versus ranitidine, misoprostol and sucralfate shows a therapeutic advantage in favour of the PPI. Several studies now confirm the efficacy of co-therapy with PPIs in the short- and long-term prevention of NSAID-induced upper GI injury. PPIs are more effective than histamine H_2-receptor antagonists at standard dosages in reducing the risk of gastric and duodenal ulcer, and are superior to misoprostol in preventing duodenal but not gastric lesions. However, when balancing effectiveness and tolerance,

PPIs may be considered the treatment of choice in the short- and long-term prevention of NSAID-related mucosal lesions.

To date, there are only a few published articles dealing with the role of PPIs in the prevention of upper GI complications. Recent epidemiological and interventional studies provide some evidence that PPIs are of benefit. However, more controlled studies using clinical outcomes are needed to establish the best management strategy (PPIs combined with traditional NSAIDs or with cyclo-oxygenase-2 selective inhibitors) especially in patients with multiple risk factors, in patients using concomitant low-dose aspirin, corticosteroids or anticoagulants (high risk group), or in patients with a history of ulcer complications (very high risk group).

Furthermore, it should be underlined that *Helicobacter pylori* infection positively interacts with the gastroprotective effect of PPIs; therefore, the true efficacy of these drugs in preventing NSAID-related ulcer complications should be reassessed without the confounding influence of this microorganism.

Although adverse effects only occur in a small proportion of individuals, widespread use of NSAIDs has resulted in a substantial number of individuals experiencing serious gastrointestinal (GI) complications. It is estimated that 10–20% of NSAID users report dyspeptic symptoms, and 5–15% of rheumatoid arthritis (RA) patients taking NSAIDs are expected to discontinue medication because of dyspepsia.[1,2] It is now well established that the point prevalence of peptic ulcer disease in patients receiving conventional NSAID therapy ranges between 10% and 30%, which is a 10- to 30-fold increase over that found in the general population.[3]

In a study that examined the prevention of NSAID-related ulcer complications in 8843 RA patients, it was reported that, over a 6-month trial period, 0.74% of patients (or 1.5% annually) in the placebo group experienced upper GI complications (UGICs).[4] More comprehensive information regarding both RA and osteoarthritis (OA) patients comes from a recent meta-analysis[5] of NSAIDs versus placebo in randomized clinical trials and three previously unpublished US FDA, placebo-controlled, randomized trials, nine cohort studies and 23 case control studies sufficiently clinically homogeneous to be pooled. The pooled odds ratio (OR) from 16 NSAID versus placebo clinical trials (comprising 4431 patients) was 5.36 (95% CI 1.79, 16.1). The pooled relative risk (RR) of UGICs from nine cohort studies (comprising over 750 000 person-years of exposure) was 2.7 (95% CI 2.1, 3.5). The pooled OR of UGICs from 23 case control studies using age and sex matching (representing 25 732 patients) was 3.0 (95% CI 2.5, 3.7).

The mortality of hospitalized patients remains about 5–10%, with an expected annual death rate of 0.08%.[6] However, this may represent an overestimate because these data were extrapolated to a non-age-adjusted RA population, a group with higher all-cause mortality than the population in general. In a recent study using comprehensive data from the Spanish National Health system, the rate of NSAID-associated deaths was 15.3 per 100 000 users.[7] In a recent study from the UK, it has been calculated that approximately 2000 patients per annum may die as a result of NSAID-induced ulcer bleeding and perforation.[8]

Cyclo-oxygenase [COX]-2 inhibitors (coxibs) are less likely than traditional NSAIDs to cause serious GI complications. The data from interventional controlled trials comparing coxibs with placebo or traditional NSAIDs indicate some increase in GI risk, albeit less than is seen with traditional NSAIDs.[9]

In a case control study,[10] the adjusted RR of UGICs associated with current use was 3.7 (95% CI 3.1, 4.3) for traditional NSAIDs and 2.6 (95% CI

1.9, 3.6) for coxibs. Concomitant use of aspirin reduced the superior GI safety of coxibs over traditional NSAIDs. The estimate of RR associated with coxibs was 0.8 (95% CI 0.6, 1.1) compared with current use of traditional NSAIDs, and, among nonusers of aspirin, the corresponding estimate of RR associated with coxibs was 0.6 (95% CI 0.4, 0.9). The evidence that using concomitant aspirin probably offsets the gastroprotective effect of coxibs has been confirmed in a recent review on GI effects of NSAIDs.[11]

Therefore, coxibs present a better upper GI safety profile than traditional NSAIDs, especially in OA patients. However, the modest reduction in risk of GI complications should be balanced against an increase in the risk of cardiovascular (CV) events.[12,13] A small increase in CV risk was also observed after use of traditional NSAIDs, which varies between individual traditional NSAIDs.[14,15]

Not all patients have the same risk of GI adverse effects. According to data in the literature, risk factors for serious upper GI events in patients taking NSAIDs include: history of previous ulcer complications, history of previous non-complicated ulcer, advanced age, concomitant use of other NSAIDs, corticosteroids, antiplatelet or anticoagulant drugs, and significant CV disability.[16] The other common risk factor is the previously mentioned concomitant use of low-dose aspirin, which has been prescribed for CV prophylaxis. This aspect complicates the management of these patients; it is not known whether concomitant low-dose aspirin use, which occurs in more than 20% of patients who need NSAIDs, will reduce the increased risk of NSAID-related CV events, but it is well known that low-dose aspirin increases the risk of GI complications in patients who use either non-selective or COX-2-selective NSAIDs.

1. Strategies to Avoid NSAID-Related Events

An obvious way to avoid GI toxicity from traditional NSAIDs is to discontinue or reduce their use. A Canadian study[17] showed that NSAIDs were prescribed unnecessarily during 41% of visits and there was an increased risk of adverse effects due to suboptimal treatment. Indeed, the guidelines developed by the American College of Rheumatology (ACR) advise initial use of paracetamol (acetaminophen) in OA patients. However, while some patients with OA may respond to analgesics alone, others will require the anti-inflammatory effect of NSAIDs to control their symptoms adequately and appropriately. In patients with RA, the ACR guidelines emphasize that an initial trial of NSAIDs is an essential component in the management of this condition.[18,19]

Thus, most patients with RA and many with OA will be unable to tolerate the substitution of a pure analgesic for the anti-inflammatory effects that are derived with NSAID use. Quality of life (QOL) issues will often not allow this substitution. Therefore, NSAIDs will frequently need to be continued in patients who may be at risk of developing NSAID-related toxicity. At present, the following three strategies have been shown to be equally effective in patients with GI risk factors:

1. Use of a coxib instead of a non-selective NSAID. Clinical trials suggest that these agents (in the absence of concomitant COX-1 inhibition with aspirin) substantially reduce the risk of upper and lower GI events.[20-25] As a result, use of these agents increased rapidly, even among patients at relatively low risk for NSAID-related adverse events.[26] Perhaps surprisingly, the introduction of coxibs has been accompanied by an increase in the absolute numbers of patients with GI bleeding. In a population-based study conducted by Mamdani et al.[27] using a large administrative healthcare database, a 41% increase in NSAID use (entirely due to an increase in coxib use) was accompanied by a 10% increase in hospitalization for upper GI bleeding (UGIB). These data suggest that the introduction of coxibs led to the exposure of high-risk patients to NSAIDs, frequently in the absence of appropriate gastroprotective therapy; these are patients who might not have otherwise received NSAIDs.
2. Use of a traditional NSAID plus a proton pump inhibitor (PPI) or misoprostol.[28]
3. Use of a coxib plus a PPI.[29]

In patients with high GI risk, the latter two strategies seem appropriate. In the individual patient, the best therapeutic strategy should be based on the evaluation of the presence of both GI and CV risk factors. Emerging evidence that coxibs and some NSAIDs increase CV risk has resulted in a major clinical challenge to prescribing NSAIDs. Before prescribing anti-inflammatory therapy, it is now necessary to assess not only the GI risk but also the CV risk of individual patients.

2. Role of Proton Pump Inhibitors (PPIs) in Patients Taking NSAIDs: Which Rationale?

2.1 Acid Suppression

Intragastric acidity has been shown to influence the severity of NSAID-induced mucosal damage in the stomach and duodenum. In an experimental setting, the extent of gastric mucosal injury following luminal or parenteral administration of NSAIDs has been shown to be highly pH dependent.[30,31] In healthy volunteers, a significant inverse relationship has been observed between fasting gastric pH and the severity of naproxen-induced damage.[32] In addition, prostaglandin depletion induced by NSAIDs leads to an increase in gastric acid synthesis and, therefore, a reduction in the pH of the gastric lumen.[33] The NSAID-associated increase in gastric acidity occurs rapidly following the start of therapy.[34] Therefore, there is a close interaction between gastric acid and NSAIDs, which exacerbates mucosal damage.

Increased gastric acidity may contribute to NSAID-induced damage in a number of ways: (i) enhancement of NSAID gastric absorption;[35] (ii) amplification of mucosal injury induced by endogenous prostaglandin deficiency;[36] (iii) activation of pepsin, the proteolytic activity of which may add to damage;[35] (iv) delay of the process of ulcer healing by interfering with cell proliferation at the ulcer crater and probably contributing to the inhibition of angiogenesis in the ulcer bed;[37] and (v) impairment of haemostasis causing clot digestion, thus enhancing the risk of mucosal bleeding. Green et al.[38] showed that platelet aggregation and plasma coagulation were both virtually abolished at pH 5.4. Previously formed platelet aggregates disaggregated at a slightly acid pH, platelet disaggregation being further enhanced by pepsin. Therefore, the maintenance of a high intragastric pH above 6.0 would theoretically stabilize the adherent blood clot at the ulcer base.

The most convincing evidence that gastric acidity is a contributing factor to NSAID-associated mucosal damage and upper GI symptoms is found in the results of clinical studies that show acid-suppression therapies to be effective in the prevention and treatment of these outcomes.

PPIs seem to be the best candidates to hinder the acidic mechanism of NSAID-induced gastroduodenal lesions. PPIs inhibit gastric acid secretion and raise intragastric pH, decreasing the damaging potential of NSAIDs. PPIs inhibit the final step of acid secretion, the gastric acid pump. All currently available PPIs are substituted benzimidazoles. They share a similar core structure, 2-pyridyl-methylsulfinyl benzimidazole; however, they differ according to their chemical stability under acidic and neutral pH, the cysteines of the proton pump with which they bind, activation under acidic conditions, dissociation constant values, half-lives, bioavailability and metabolism.

Whether the differences in chemical structure of PPIs translate into differences in clinical efficiency is still a matter of debate, although in a recent short-term (up to 5 days) comparative study, esomeprazole 40 mg treatment provided significantly greater gastric acid suppression than lansoprazole 30 mg or pantoprazole 40 mg (all once daily) in patients receiving traditional NSAIDs or coxibs.[39]

PPIs inhibit only active proton pumps. Because not all pumps are active at any given time, a single dose of a PPI does not inhibit all pumps and does not result in profound inhibition of acid secretion. Therefore, acid secretion will be inhibited with subsequent PPI doses, taking 5–7 days to achieve a steady state with a PPI. Because of this, if PPIs are used on an 'as needed' basis,

acid inhibition may be inadequate and clinically disappointing in preventing gastroduodenal damage from NSAIDs.

2.2 Cytoprotective Effect

Acid suppression could be only one of the many mechanisms by which PPIs protect the gastroduodenal mucosa. There is also evidence to suggest that these drugs can activate gastric protective mechanisms independent of acid reduction.[40,41] For instance, in previous studies, omeprazole and lansoprazole prevented gastric injury elicited by acidified ethanol or haemorrhagic shock through an enhancement of mucosal defence.[40] At present, a large variety of endogenous factors, including prostaglandins, growth factors, digestive hormones, sensory peptides, nitric oxide and sulfhydryl compounds, have been implicated in the mechanisms through which the gastric mucosa counteracts ulcerative stimuli,[42] and some of these factors have been suggested to account for the gastroprotective effects of PPIs.[40,41] Nevertheless, the possible contribution of acid-independent mechanisms to the protective effects of these drugs against NSAID-induced gastric injury remains to be clarified. In the experimental setting, omeprazole has been shown to inhibit the production of toxic oxidants by activated neutrophils. The action of omeprazole may be associated with a malfunction of lysosomal oxidant-producing enzymes as a result of an elevated intralysosomal pH.[43] Further studies have documented that, in addition to the inhibition of acid secretion, the protective effects of lansoprazole against NSAID-induced gastric damage depends on a reduction in mucosal oxidative injury, which is also responsible for an increase in sulfhydryl radical bioavailability. It has also been suggested that lansoprazole does not influence the down-regulation of gastric prostaglandin production associated with NSAID treatment.[44] Lastly, in experimental animals and in humans, rabeprazole significantly increased production of gastric mucus and mucin in basal conditions and after administration of naproxen.[45,46]

3. Healing Phase

3.1 Dyspepsia

Dyspeptic symptoms, including heartburn, anorexia, abdominal pain and distension, have been reported in 5–20% of patients taking NSAIDs. While common, dyspepsia correlates poorly with the development of ulcers and has not been found to be a risk factor in many observational studies.

Nevertheless, upper GI symptoms, together with the underlying inflammatory disease, lead to substantial reductions in health-related QOL (HR-QOL) in patients taking long-term NSAID therapy[47] and often lead to dose reduction or discontinuation of NSAID treatment.[48] Treatments that relieve upper GI symptoms associated with NSAIDs may thus allow patients to continue therapy with these drugs. Furthermore, among patients with a history of ulcer bleeding who received celecoxib or diclofenac plus omeprazole, those who experienced dyspepsia during treatment were more likely to develop recurrent ulcers compared with patients who remained asymptomatic (hazard ratio 5.3; 95% CI 2.6, 10.8).[49]

Thus, treatments that relieve upper GI symptoms associated with NSAIDs, in high-risk patients in particular, may allow patients to continue therapy with these drugs.

There is a body of evidence that cimetidine,[50] ranitidine[51] and famotidine[52] are of benefit for symptomatic relief of dyspeptic symptoms. However, Singh and Triadafilopoulus[6] reported that asymptomatic RA patients who were taking histamine H_2-receptor antagonists developed significant UGICs more often than those not taking these medications. This surprising observation might be due to the masking of dyspeptic symptoms associated with mucosal damage by the antisecretory drugs.

Two studies comparing omeprazole with ranitidine[53] or misoprostol[54] have shown that omeprazole provided greater relief of dyspeptic symptoms than ranitidine. Patients receiving the PPI reported a greater improvement in QOL than patients receiving misoprostol. The role of esomeprazole was evaluated in patients with upper GI symptoms taking NSAIDs, including

Table I. Trial acronyms and full names

Acronym	Trial name
ASTRONAUT	Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment
NASA1	Nexium Anti-inflammatory Symptom Amelioration
OMNIUM	Omeprazole versus Misoprostol for NSAID Induced Ulcer Management
PLUTO	Prevention of Latent Ulceration Treatment Options
SPACE1	Symptom Prevention for NSAID Ulcers and Symptoms
VENUS	Verification of Esomeprazole for NSAID Ulcers and Symptoms

selective coxibs.[55,56] In two identical, multinational, multicentre, double-blind studies (NASA1 and SPACE1 [see table I for full trial names]),[55] a total of 608 and 556 continuous NSAID users, free of gastroduodenal ulcers, erosive esophagitis and *Helicobacter pylori*, were enrolled. The patients were randomized to receive esomeprazole 20 mg or 40 mg, or placebo once daily for 4 weeks. The primary variable was the patient-reported change in the upper GI symptom (pain, discomfort or burning in the upper abdomen) score on a 7-graded severity scale (0–6) from the 7 days prior to treatment to the last 7 days in the study. Esomeprazole was associated with highly significant symptom improvement compared with placebo. Symptom improvements were 2.30 mean (standard deviation [SD] 1.63) with esomeprazole 20 mg and 2.03 (SD 1.56) with esomeprazole 40 mg versus 1.64 (SD 1.57) with placebo in NASA1, and 2.17 (SD 1.34] and 2.12 (SD 1.48) versus 1.56 (SD 1.26), respectively, in SPACE1 (all placebo comparisons at least $p < 0.001$). Esomeprazole improved symptoms in patients taking selective coxibs, with changes of 2.21 (SD 1.46) and 1.92 (SD 1.38) versus 1.64 (SD 1.46) in NASA1, and 2.20 (SD 1.26) and 2.24 (SD 1.62) versus 1.58 (SD 1.37) in SPACE1 (all placebo comparisons at least $p < 0.05$), as well as those receiving non-selective NSAIDs. Esomeprazole was well tolerated and associated with significant improvements in HR-QOL. Furthermore, the study provided some of the best evidence available of the effectiveness of PPI therapy in reducing symptoms that can occur irrespective of the type of NSAID.

Similar data were observed in a *post hoc* analysis of other studies that aimed to evaluate the role of esomeprazole versus placebo (PLUTO/VENUS studies) and versus ranitidine.[56]

3.2 Mucosal Lesions

All traditional antisecretory drugs show efficacy in healing NSAID-induced mucosal lesions. After discontinuation of NSAIDs, healing was achieved with the usual therapeutic regimens and in comparable times to those seen in peptic ulcer. Healing rates for gastric lesions range from 60–65% with cimetidine 300 mg four times daily for 4–6 weeks,[57-61] to 89–95% with famotidine 40 mg at night for 8 weeks,[62,63] and up to 95% and 100% with ranitidine 150 mg twice daily for 8 and 12 weeks, respectively.[64] The healing rates for duodenal lesions, ranged from 35%[65] to 59%[66] after 4 weeks of treatment with ranitidine to 100% after 8 weeks treatment with cimetidine.[60]

Profound acid suppression with a PPI appears most effective in healing ulcers during continued NSAID use, accelerating the slow healing observed with H_2-receptor antagonists.

In a multicentre study, a subgroup of 68 gastric ulcer patients who continued using NSAIDs showed rapid ulcer healing when receiving omeprazole 20 and 40 mg/day, with a therapeutic advantage after 8 weeks of 31% and 43%, respectively, compared with ranitidine 300 mg.[67] In a larger population of 541 patients, two doses of omeprazole (20 and 40 mg/day) were compared with ranitidine 150 mg twice daily. The PPI was significantly more effective than the H_2-receptor antagonist, with a therapeutic success (ulcer healing) of 84%, 87% and 67%, respectively, in gastric-ulcer patients, and 92%, 88% and

81%, respectively, in duodenal ulcer patients.[53] The clinical effectiveness of omeprazole was also documented in controlled studies with cytoprotective drugs. A therapeutic gain of 18% in gastric ulcer patients and 22% in duodenal ulcer patients taking NSAIDs was seen compared with sucralfate.[68] In contrast, in the OMNIUM study,[46] no difference was seen between omeprazole (20 and 40 mg/day) and misoprostol (200 μg four times daily) in terms of ulcer healing.

Similar results were seen with lansoprazole (15 or 30 mg/day) when compared with ranitidine (150 mg twice daily). Both doses of the PPI were found to be significantly more effective than ranitidine for providing healing of gastric ulcers after both 4 and 8 weeks of treatment while continuing NSAIDs. The 8-week gastric ulcer healing rates were 73%[69] and 74%[70] in patients treated with lansoprazole 30 mg, relative to respective healing rates of 53% ($p < 0.01$) and 50% ($p < 0.001$) in patients treated with ranitidine 150 mg twice daily.

The usefulness of pantoprazole in healing ulcers associated with ongoing NSAID therapy was tested in a comparative study in which 120 *H. pylori*-negative patients who had NSAID-associated ulcers were randomized to receive pantoprazole 40 mg/day, omeprazole 20 mg/day or misoprostol 800 μg/day while taking NSAIDs.[71] Pantoprazole appeared to heal ulcers more rapidly than omeprazole or misoprostol, although all the ulcers had healed after 8 weeks of therapy.

Two studies compared esomeprazole (20 or 40 mg once daily) with ranitidine.[72,73] In the first study,[72] gastric ulcer healing occurred in significantly higher proportions of patients treated with either 20- or 40-mg dose of esomeprazole compared with the ranitidine treatment group at both the 4- and 8-week assessments. At the end of the 8-week treatment period, the healing rate was 74% with ranitidine compared with 88% with esomeprazole 20 mg ($p < 0.001$) and 92% with esomeprazole 40 mg ($p < 0.001$). In the latter study[73] by the same authors, a significant difference in favour of both doses of esomeprazole was seen only after 4 weeks; after 8 weeks, the healing rates were 84.8% and 85.7% for esomeprazole 20 and 40 mg/day, and 76.3% for ranitidine 150 mg twice daily (difference not significant).

In a double-blind, placebo-controlled, randomized trial, 150 patients using low-dose aspirin (80 mg/day) with upper GI symptoms who had been admitted at a Coronary Care Unit were assigned to treatment with rabeprazole (20 mg once daily) or placebo for 4 weeks. At 4 weeks after randomization, 34 of 73 patients assigned to rabeprazole therapy (47%) compared with 30 of 70 patients given placebo (43%) reported complete upper GI symptom relief ($p = 0.54$).[74] Table II shows the endoscopic outcome, expressed as percentage of healing, of the fully published studies comparing PPIs with H_2-receptor antagonists and cytoprotective drugs in patients continuing NSAID therapy.

4. Prevention Phase

4.1 Short-Term Studies (Up to 1 Month)

Whether or not PPIs protect against acute NSAID damage in humans has been examined in a number of short-term trials. In most instances, the PPI used was omeprazole. The largest of the short-term studies recruited patients with arthritis who were treated with omeprazole or placebo concurrently with an NSAID for 3 weeks.[75] All the other studies used healthy volunteers who were given an NSAID (mostly aspirin) as a single dose or for up to 2 weeks. All studies demonstrated protection against NSAID gastric damage when co-therapy was given with either omeprazole or lansoprazole.

A placebo-controlled study assessed gastric damage by using a gastric lavage technique to measure gastric microbleeding after aspirin. Blood loss was reduced by about 80% when omeprazole 20 or 80 mg/day was given for 1 week, then aspirin 900 mg was administered daily on the last 2 days. A significant negative correlation was found between the volume of microbleeding and the intragastric pH achieved.[76]

All the other studies measured gastric damage endoscopically. Usually only erosions are found during such short-term studies and these were quantified on an ordinal scale in each report.

Table II. Endoscopic outcome (percentage of healing gastric ulcers [GUs] or duodenal ulcers [DUs]) in fully published controlled studies comparing esomeprazole, omeprazole, lansoprazole and pantoprazole with ranitidine, sucralfate and misoprostol in patients continuing NSAID therapy

Study (year)	Therapy	Follow-up (wk)	GU (% of healing)	DU (% of healing)	GU + DU (% of healing)
Walan et al.[67] (1989)	Omeprazole 20 mg od	8			89
	Omeprazole 40 mg od				96
	Ranitidine 300 mg od				85
Yeomans et al.[53] (1998)	Omeprazole 20 mg od	8	84**	92****	
	Omeprazole 40 mg od		87***	88****	
	Ranitidine 150 mg bid		64	81	
Agrawal et al.[69] (2000)	Lansoprazole 15 mg od	8	81*		
	Lansoprazole 30 mg od		85*		
	Ranitidine 150 mg bid		53		
Bianchi Porro et al.[68] (1998)	Omeprazole 20 mg od	8	87†	95†	
	Sucralfate 2 g bid		52	73	
Hawkey et al.[54] (1998)	Omeprazole 20 mg od	8	87‡	93‡‡	
	Omeprazole 40 mg od		80	89‡‡	
	Misoprostol 200 μg qid		73	77	
Olteanu et al.[71] (2000)	Pantoprazole 40 mg od	8			100
	Omeprazole 20 mg od				100
	Misoprostol 200 μg qid				100
Campbell et al.[70] (2002)	Lansoprazole 15 mg od	8			66
	Lansoprazole 30 mg od				74
	Ranitidine 150 mg bid				50
Goldstein et al.[72] (2005)	Esomeprazole 20 mg od	8			88***
	Esomeprazole 40 mg od				92***
	Ranitidine 150 mg bid				74
Goldstein et al.[73] (2007)	Esomeprazole 20 mg od	8			85
	Esomeprazole 40 mg od				86
	Ranitidine 150 mg bid				76

bid = twice daily; **od** = once daily; **qid** = four times daily; * $p < 0.05$, ** $p = 0.03$, *** $p < 0.01$, **** $p < 0.001$ vs ranitidine; † $p < 0.05$ vs sucralfate; ‡ $p = 0.004$, ‡‡ $p < 0.001$ vs misoprostol.

In placebo-controlled studies, protection against erosions was seen in 79–100% of patients treated with omeprazole 20–40 mg/day.[77-80] A similar protection was seen with omeprazole 60 mg/day[81] and in other studies with lansoprazole 30 mg/day[82] and 15 mg/day,[83] or with rabeprazole 20 mg/day.[84] Two studies included arms treated with ranitidine 300 mg/day, which did not confer significant protection.[78,83] It is uncommon for ulcers to develop during such short-term administration of NSAIDs. However, a few acute ulcers were seen in the studies by Bianchi Porro et al.[75] and Scheiman et al.,[77] who documented that omeprazole 20 or 40 mg/day reduced the incidence by 80–100% although the numbers were small and significance was reached only in the larger study.[75] In the study by Scheiman et al.,[77] no ulcers occurred in the omeprazole group, but 15% of the patients developed them while taking placebo plus aspirin ($p < 0.01$).

PPIs were also compared with eradication therapy in *H. pylori*-positive patients aged over 60 years taking NSAIDs and with a history of peptic ulcer. After a basal endoscopy, patients were randomized to a 1-week eradication regimen plus placebo for 3 weeks (group 1) or pantoprazole 40 mg/day for 4 weeks (group 2). A significantly higher incidence of severe gastroduodenal damage

was found in group 1 than in group 2 (29% vs 9%; $p < 0.05$). The percentage of *H. pylori*-negative subjects after 4 weeks was 89% in group 1 and 52% in group 2 ($p = 0.0009$).[85]

Of interest are the results of a case control study[86] performed in elderly patients requiring treatment with NSAIDs or aspirin for a short period of time. In a population of 325 patients, PPI treatment was associated with a reduced risk of peptic ulcer in the acute phase (OR = 0.70; 95% CI 0.24, 2.04). The absolute risk of peptic ulcer was reduced by 36.6%. The number needed to treat to avoid one peptic ulcer was three. The authors' conclusions were that "PPI co-therapy seems advisable in symptomatic elderly patients who need to be treated with NSAIDs for a short period of time".

4.2 Long-Term Studies

4.2.1 PPIs versus Placebo

To date, five controlled studies comparing PPI therapy with placebo for 3 months or longer[75,87-90] and one case control study[86] have been published. Despite varying somewhat in design, the two larger studies with omeprazole 20 mg/day both reported reductions of more than 70% in overall ulcer rates (gastric plus duodenal) when the PPIs were co-prescribed with the NSAID.[86,87] A placebo arm was also included in the large misoprostol versus omeprazole trial described in section 4.2.3.[54] In a smaller study by Bianchi Porro et al.,[89] pantoprazole 40 mg once daily was more effective than placebo. After 12 weeks of treatment, the proportions of patients in remission (without mucosal ulcers) were 72% and 59%, respectively.

The data on the site of ulcer occurrence in these studies raise the possibility that PPIs may protect the duodenum a little better than the stomach, although the differences do not approach statistical significance.

The gastroprotective role of esomeprazole was evaluated in two identically-designed, double-blind, placebo-controlled, randomized, multicentre studies: VENUS (US) and PLUTO (multinational).[90] A total of 844 and 585 patients, respectively, requiring daily NSAIDs, including coxibs, were randomized to receive esomeprazole (20 or 40 mg/day) or placebo for 6 months. In the VENUS study, the life table estimated the proportion of patients who developed ulcers over 6 months to be 20.4% with placebo, 5.3% with esomeprazole 20 mg/day ($p < 0.001$) and 4.7% with esomeprazole 40 mg/day ($p < 0.0001$). In the PLUTO study, the estimates were 12.3% with placebo, 5.2% with esomeprazole 20 mg/day ($p = 0.018$) and 4.4% with esomeprazole 40 mg/day ($p = 0.007$). Significant reductions were observed for users of both non-selective NSAIDs and coxibs. Pooled ulcer rates for patients using coxibs ($n = 400$) were 16.5% with placebo, 0.9% with esomeprazole 20 mg ($p < 0.001$) and 4.1% with esomeprazole 40 mg ($p = 0.002$). Esomeprazole was well tolerated and associated with better symptom control than placebo. The number needed to treat to prevent a gastric or duodenal ulcer occurring within 6 months in one patient was calculated as nine and eight for esomeprazole 20 and 40 mg/day, respectively.[91]

4.2.2 PPIs versus Histamine H_2-Receptor Antagonists

The well known ASTRONAUT study[53] recruited patients continuing treatment with NSAIDs who had peptic ulcer or more than ten gastric or duodenal erosions. In the healing phase, patients were treated with omeprazole or raniditine; those patients whose lesions healed were randomized to either omeprazole 20 mg/day or ranitidine 150 mg twice daily and assessed after 6 months. Omeprazole was more effective, with 94% of patients remaining ulcer-free overall compared with 79.5% receiving ranitidine.

Again, there was a trend to higher protection against duodenal ulcer: only 1 duodenal ulcer (0.5%) compared with 11 gastric ulcers (5.2%) were noted during omeprazole maintenance treatment, whereas with ranitidine, there were 9 duodenal and 35 gastric ulcers (4.2% and 16.3%, respectively). As expected, both these acid-suppressant drugs were well tolerated.

In a small controlled study from Japan,[92] lansoprazole 15 mg once daily was compared with famotidine 20 mg once daily. The peptic ulcer onset rate was 8% (1 of 13) in the famotidine group and 15% (2 of 13) in the lansoprazole group, indicating no significant differences between the two drugs.

4.2.3 PPIs versus Misoprostol

The OMNIUM study[54] was of similar design to ASTRONAUT,[53] comparing omeprazole with misoprostol in the healing phase and adding a placebo arm to the maintenance phase. Patients who healed after 8 weeks of therapy with omeprazole (20 or 40 mg/day) or misoprostol (200 μg four times daily) were randomized to omeprazole 20 mg/day, misoprostol 200 μg twice daily or placebo for 6 months. Overall, ulcer recurrence rates were 15% in patients receiving omeprazole, 21% in patients receiving misoprostol and 44.5% in patients receiving placebo. Again, examination of ulcer-site data is of interest. Misoprostol was better than omeprazole in preventing gastric ulcers (10% and 13% recurrence, respectively), but omeprazole appears superior for prophylaxis of duodenal ulcer (3% recurrence vs 10% for misoprostol).

In terms of adverse effects, misoprostol was discontinued more often than either omeprazole or placebo (16.8% vs 12.1% vs 10.3%, respectively; $p < 0.01$), particularly as a result of an adverse event (7.7% vs 3.9% vs 1.9%; $p < 0.02$). Rates of individual adverse effects were not dramatically different between the agents (e.g. misoprostol was associated with diarrhoea in 8.4% of patients compared with 7.6% of patients taking omeprazole), although this may be a function of sample size.

Similar results were observed when pantoprazole 20 mg once daily was compared with misoprostol 200 μg twice daily in 515 RA patients requiring continuous traditional NSAID therapy for at least 6 months.[93] Pantoprazole was superior to misoprostol with regards to the occurrence of dyspeptic symptoms, the proportion of mucosal ulcers or instances of more than ten erosions at endoscopic control, and the incidence of adverse effects leading to study termination. The proportions of mucosal lesions at 3 and 6 months were, respectively, 2% and 5% (pantoprazole), and 5% and 14% (misoprostol) [$p < 0.005$ after 6 months].

Graham et al.[94] compared two doses of lansoprazole (15 and 30 mg/day) with full-dose misoprostol (200 μg four times daily) in *H. pylori*-negative, long-term NSAID users who had a history of gastric ulcer. The results showed that full-dose misoprostol was more effective than either dose of lansoprazole for the prevention of gastric ulcer on per-protocol analysis. By week 12, the percentages of gastric ulcer-free patients were as follows: placebo 51% (95% CI 41.1, 61.3); misoprostol 93% (95% CI 87.2, 97.9); lansoprazole 15 mg/day 80% (95% CI 72.5, 87.3); and lansoprazole 30 mg/day 82% (95% CI 75.0, 89.6). However, there was no practical therapeutic advantage of misoprostol over lansoprazole because of the high withdrawal rate in the misoprostol group due to poor compliance and adverse effects.

A body of meta-analytic evidence underlines the respective roles of PPIs, H_2-receptor antagonists and misoprostol in the prevention of symptoms and of endoscopic markers of upper GI adverse effects related to NSAIDs.[95-99]

The meta-analysis by Leandro et al.[97] showed that all doses of misoprostol and PPIs were more effective than H_2-receptor antagonists in the prevention of severe gastric and duodenal damage. In healthy volunteers, the active drug treatment induced a significant prevention of severe gastric (misoprostol risk difference [RD] 69% [95% CI 60.3, 77.7]; H_2-receptor antagonist RD 38.3% [95% CI 17.8, 58.9]; PPI RD 43% [95% CI 28.2, 57.7]) and duodenal damage (misoprostol RD 22.3% [95% CI 13.6, 31]; H_2-receptor antagonist RD 13.2% [95% CI 5.2, 21.3]; PPI RD 17.7% [95% CI 3.5, 31.8]).

A more recent meta-analysis[98] of randomized controlled trials versus placebo in long-term NSAID users showed that PPIs significantly reduce the risk of endoscopically detected duodenal and gastric ulcers, standard doses of H_2-receptor antagonists were effective in reducing the risk of endoscopic duodenal ulcers (RR 0.36; 95% CI 0.18, 0.74), but not gastric ulcers (RR 0.73; 95% CI 0.50, 1.09) and misoprostol 800 μg/day was superior to 400 μg/day for the prevention of endoscopic gastric ulcers, but not duodenal ulcers.

Table III shows the endoscopic outcome, expressed as percentage of relapse, of the fully published studies comparing PPIs to H_2-receptor antagonists and cytoprotective drugs.

Table III. Long-term, preventive, controlled, prospective trials with proton pump inhibitors. Endoscopic outcome in fully published comparative studies with placebo, misoprostol, ranitidine and famotidine

Study (year)	Therapy	Follow-up (wk)	No. of GU + DU at the end of follow-up (%)
Ekström et al.[88] (1996)	Omeprazole 20 mg od	12	5*
	Placebo		17
Bianchi Porro et al.[89] (1998)	Pantoprazole 40 mg od	12	28 (ns)
	Placebo		41
Cullen et al.[87] (1998)	Omeprazole 20 mg od	24	4***
	Placebo		17
James et al.[90] (2006)	Esomeprazole 20 mg od	24	6*****
	Esomeprazole 40 mg od		5*****
	Placebo		21
Yeomans et al.[91] (2004)	Esomeprazole 20 mg od	24	5****
	Esomeprazole 40 mg od		4****
	Placebo		12
Yeomans et al.[53] (1998)	Omeprazole 20 mg/day	24	28†
	Ranitidine 150 mg/day		41
Miyake et al.[92] (2005)	Lansoprazole 15 mg od	12	15 (ns)
	Famotidine 20 mg od		8
Hawkey et al.[54] (1998)	Omeprazole 20 mg/day	24	39‡*****
	Misoprostol 400 μg/day		52*****
	Placebo		73
Graham et al.[94] (2002)	Lansoprazole 15 mg od	12	20**
[only GU patients were evaluated]	Lansoprazole 30 mg od		18**
	Misoprostol 200 μg qid		7**
	Placebo		49
Stupnicki et al.[93] (2003)	Pantoprazole 20 mg od	24	5‡
	Misoprostol 200 μg bid		14

bid = twice daily; **DU** = duodenal ulcer; **GU** = gastric ulcer; **ns** = p-value not significant ; **od** = once daily; **qid** = four times daily; * $p < 0.05$, ** $p < 0.01$, *** $p = 0.004$, **** $p = 0.007$, ***** $p < 0.001$ vs placebo; † $p = 0.004$ vs ranitidine; ‡ $p = 0.001$ vs misoprostol.

5. Upper Gastrointestinal Complications

Most studies focusing on the prevention of NSAID-associated GI adverse effects with PPIs are endoscopy studies, which provide limited information on clinical outcome. Data derived from endoscopy studies can be considered subclinical markers of the effect of these drugs for more concrete endpoints such as UGICs. A recent meta-analysis of clinical trials reported that PPI therapy is very effective in reducing the risk of symptomatic ulcers, but there was no statistically significant effect on UGIB.[99,100]

To date, there are only a few epidemiological and interventional studies in the literature dealing with the role of PPIs in the prevention of UGICs.

5.1 Interventional Studies

In a population of patients with *H. pylori* infection and a history of UGIB who were taking low-dose aspirin or non-aspirin NSAIDs, the authors[101] evaluated whether eradication of the infection or omeprazole treatment was more effective in preventing recurrent bleeding. After healing, the patients were randomly assigned to receive omeprazole 20 mg/day for 6 months or eradication therapy for 1 week followed by placebo for 6 months. Among those taking aspirin, the probability of recurrent bleeding during the 6-month period was 1.9% for patients who received eradication therapy and 0.9% for patients who received omeprazole (difference not significant).

Among users of other NSAIDs, the probability of recurrent bleeding was 18.8% for patients receiving eradication therapy and 4.4% for those treated with omeprazole (p = 0.005). Therefore, the eradication of *H. pylori* was equivalent to treatment with omeprazole in preventing recurrent bleeding in low-dose aspirin recipients, but long-term omeprazole was significantly superior to the eradication of *H. pylori* in preventing recurrent bleeding in patients who are taking other NSAIDs.

The efficacy of PPIs for the prevention of recurrent ulcer complications associated with long-term, low-dose aspirin was studied in a trial of 123 patients with *H. pylori* infection and ulcer complications. After the ulcers had healed and the *H. pylori* infection was eradicated, the patients were randomly assigned to treatment with lansoprazole 30 mg/day or placebo in addition to 100 mg/day of aspirin for 12 months. Ulcer complications recurred in 1.6% and 14.8% of patients in the lansoprazole and placebo groups, respectively (p = 0.008).[102]

Further studies have evaluated the relative efficacies of the currently recommended strategies for prevention of UGICs in NSAID users including co-therapy with PPIs and traditional NSAIDs or selective coxibs.

Two randomized trials[103,104] have directly compared celecoxib 200 or 400 mg/day with diclofenac 150 mg/day plus omeprazole 20 mg/day or with naproxen 750 mg/day plus lansoprazole 30 mg/day. Both studies were conducted in patients with a previous ulcer bleed and who needed NSAIDs for arthritis. In the first study, only *H. pylori*-negative patients were recruited, while the second study included both *H. pylori*-positive and -negative patients, and eradication therapy was administered to positive patients. After ulcer healing, patients were randomized to treatments over 6 months. Rebleeding occurred in 4.9% of patients in the celecoxib group and 6.4% in the diclofenac plus omeprazole group during a 6-month follow-up,[103] and in 3.7% of patients in the celecoxib group compared with 6.3% in the naproxen plus lansoprazole group.[104] These data demonstrate that coxibs and traditional NSAIDs plus PPIs provide similar gastroprotection in patients at high risk for bleeding, but that neither regimen can completely protect patients at high risk from recurrent ulcer complications.

Perhaps more promising were the results of a study from Hong Kong,[29] which compared the effectiveness of the combination of celecoxib (200 mg twice daily) and esomeprazole (20 mg once daily) with celecoxib alone for prevention of recurrent ulcer bleeding. The primary endpoint was recurrent ulcer bleeding during treatment or within 1 month of the end of treatment. Combination treatment was more effective than celecoxib alone for prevention of ulcer bleeding in patients at high risk. The 13-month cumulative incidence of the primary endpoint was 0% in the combined-treatment group and 12 (8.9%) in the control group (95% CI 4.1, 13.7; p = 0.0004). The median follow-up was 13 months (range 0.4–13.0). Discontinuation of treatment and the incidence of adverse events were similar in the two treatment groups.

5.2 Epidemiological Studies

Cohort studies[105-109] and case control studies[110-114] perhaps provide the majority of evidence in determining the proper role for the different gastroprotective strategies in the prevention of UGICs.

In the first cohort study,[105] 952 patients who received maintenance treatment with H_2-receptor antagonists or omeprazole after an episode of UGIB were followed-up for a mean period of 33 months. Fewer than 10% of the cohort had a recurrent episode of bleeding. In a subgroup of NSAID users, the concomitant use of omeprazole was associated with a lower risk of bleeding (RR 0.0; 95% CI 0.0, 1.0). These data are consistent with those of other studies.

A Spanish study[106] included 247 consecutive high-risk patients who had a clinical indication for long-term treatment with either low-dose aspirin (78.9% of patients) or non-aspirin NSAIDs combined with omeprazole therapy. In addition to a recent history of peptic ulcer bleeding, all patients had at least one other risk factor and 112 (45.3%) had three or more risk factors. Three patients taking low-dose aspirin developed

upper GI re-bleeding (1.2%; 95% CI 0.3, 3.5; 1.0 event/100 patients/year). Two additional patients receiving non-aspirin NSAID therapy developed a lower GI bleeding event (0.81%; 95% CI 0.04, 3.12%; 0.67 events/100 patients/year).

Ray and co-workers[108] retrospectively studied peptic ulcer hospitalizations due to the use of non-selective NSAIDs or coxibs in a cohort of Tennessee Medicaid patients enrolled between 1996 and 2004. For current users of either NSAIDs with gastroprotective co-therapy (PPIs, H_2-receptor antagonists or misoprostol), or coxibs with or without such co-therapy, the respective risk reductions were 39% (95% CI 16, 56), 40% (95% CI 23, 54) and 50% (95% CI 28, 66). Among current users of NSAIDs, concurrent users of PPIs had the greatest risk reduction (54%; 95% CI 27, 72), which was superior to that for coxibs alone (40%; 95% CI 23, 54) and very similar to that for concurrent users of PPIs and coxibs (50%; 95% CI 27, 66). For patients prescribed aspirin, the only gastroprotective strategy associated with a statistically significant risk reduction was concurrent addition of coxib and PPI use.[108]

The issue of the preferential strategy in preventing UGICs was further examined in a Canadian population-based retrospective cohort study,[109] which suggested that for patients requiring anti-inflammatory therapy, celecoxib alone was as safe as traditional NSAIDs combined with a PPI. The addition of a PPI to celecoxib was of significant benefit compared with celecoxib alone in patients aged >75 years. PPI therapy did not seem necessary with celecoxib for patients aged 66–74 years.

Lanas et al.[110] performed a case control study to determine the risk of bleeding in 1122 patients taking nitrovasodilators, low-dose aspirin or other NSAIDs. 135 patients (12.0%) received acid suppressants, such as a H_2-receptor antagonist or a PPI. The use of a nitrovasodilator was associated with a decreased risk of bleeding (OR 0.6; 95% CI 0.4, 0.8), as was antisecretory therapy (OR 0.6; 95% CI 0.4, 0.9).

These findings are consistent with those from other recently published epidemiological studies. Höer et al.[111] found that concomitant prescribing of a PPI with diclofenac reduced the OR of an ulcer hospitalization from 2.4 (95% CI 1.94, 3.05) to 1.3 (95% CI 0.7, 2.3). Lanas and coworkers[112] published a large case control study aimed to evaluate the effect of antisecretory drugs and nitrates on the risk of peptic ulcer bleeding associated with traditional NSAIDs, aspirin, antiplatelet agents and anticoagulants. A total of 2777 consecutive patients with UGIB (confirmed by endoscopy) were matched with 5532 controls. PPI use was associated with greater reductions among both traditional NSAIDs (RR 0.13 [95% CI 0.09, 0.19] vs RR 0.30 [95% CI 0.17, 0.53] with H_2-receptor antagonists and RR 0.48 [95% CI 0.19, 1.24] with nitrates) and aspirin at all doses (RR 0.30 [95% CI 0.20, 0.44] vs RR 0.40 [95% CI 0.24, 0.68] with H_2-receptor antagonists and RR 0.66 [95% CI 0.44, 0.98] with nitrates). Among users of low-dose aspirin, co-therapy with any of these three agents was associated with risk reduction, although only the estimates for H_2-receptor antagonists and PPIs were statistically significant. Among users of ≥500 mg/day, only current PPI use conferred protection. The overall effect was similar for both omeprazole and other PPIs available on the market (lansoprazole, pantoprazole, rabeprazole and esomeprazole).

A further analysis of the same study[113] showed that use of selective coxibs carries a modest increase in the risk of UGIB due to peptic lesions, which was entirely accounted for by a 2-fold increase with rofecoxib, whereas no increase was observed with celecoxib. The relative risk of UGIB observed with celecoxib was similar to that observed with paracetamol (acetaminophen) or the combination of PPIs with traditional NSAIDs.

More information is perhaps provided by a Canadian case control study,[114] which showed that the use of any of the commonly recommended basic gastroprotective strategies, including traditional NSAID plus PPI, traditional NSAID plus low-dose misoprostol, traditional NSAID plus low-dose misoprostol plus PPI, coxib alone, and coxib plus PPI, was associated with a significant reduction in the risk of developing an overall UGIC or a UGIC secondary to peptic ulcer disease. Coxibs were not statistically more likely to prevent UGICs than PPIs, although they were

superior to low-dose misoprostol. The combination of coxibs with a PPI was associated with the greatest degree of UGIC risk reduction.

6. Discussion

Seven years ago, the weight of evidence supporting the role of PPIs in patients taking NSAIDs prompted the contributors to a multidisciplinary expert statement[115] to recommend that ''on the basis of effectiveness and tolerance, a PPI is the treatment of choice for healing NSAID-associated ulcers, particularly gastric ulcers''. The statement also recommended that ''proton pump inhibitors use should be on a basis of risk assessment'', that ''all patients who had previous proven peptic ulceration should have prophylactic co-therapy while taking NSAIDs'' and that ''all patients with two risk factors other than past history should have prophylactic co-therapy when they use NSAIDs''.

In accordance with these conclusions, other authors[116] and an official guideline statement[117] have more recently proposed the use of PPIs as the preferential option for healing and prevention of recurrence of ulcers in patients taking both traditional NSAIDs and selective coxibs, and who have risk factors associated with more frequent or severe GI complications, including patients with previous ulcers, the elderly, those receiving concomitant corticosteroids or anticoagulants, and those in whom bleeding presents a particular risk such as patients with CV disease.

Clinical studies have not revealed any significant or consistent differences between different PPIs with regard to clinical or endoscopic endpoints. In fact, milligram for milligram, all drugs of the PPI class appear to be comparable in their clinical effects.

Both interventional and epidemiological studies provide evidence that concurrent use of a PPI is also of benefit to offset the risk of NSAID-related UGICs; however, the protective effect of a traditional NSAID plus PPI seems equivalent to that of celecoxib. 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 coxib (celecoxib) for a traditional NSAID is a safe strategy for the management of very high-risk patients or those with multiple risk factors. The available data suggest a trend in favour of adding a PPI to a coxib (celecoxib); however, further investigations are needed to evaluate the gastric safety of anti-ulcer drugs and coxibs in different risk groups using clinical outcomes rather than endoscopic mucosal injury as the endpoint.

A further topic that is still a matter of debate concerns the clinical role of PPIs in NSAID recipients with or without *H. pylori* co-infection. The potential confounding role of the microorganism has been outlined by some authors[118,119] who also observed that both endoscopic and outcome studies have rarely taken the natural history of *H. pylori* infection into account nor have the pre-existing risks been considered or stratified. In a *post hoc* subgroup analysis of endoscopic studies comparing the effect of omeprazole with misoprostol, ranitidine and placebo on the risk of ulcer development in NSAID users, a significantly different gastroprotective role of omeprazole was seen among patients with and without *H. pylori* infection – the PPI being significantly more effective than misoprostol or ranitidine in preventing duodenal or gastric ulcer, respectively, in *H. pylori*-positive patients, but not in the *H. pylori*-negative patients.[118] The difference is not easily explained. Different mechanisms were hypothesized concerning the natural history of *H. pylori*-related gastroduodenal ulcers or the different gastric acid secretory pattern in patients with or without *H. pylori* infection.

Patients with a history of *H. pylori*-related ulcer are known to have a significantly higher risk of recurrent ulcer or GI complications than non-infected patients, irrespective of NSAID use.[120,121] Therefore, NSAID users who had prior *H. pylori* ulcer disease would be expected to develop ulcers or complications during follow-up[122,123] and it would be impossible to distinguish whether the ulcer was related to the NSAID use, the *H. pylori* infection, or both. Study results have shown that cure of *H. pylori* infection reduces the antisecretory effectiveness of PPI therapy, which is probably dependent on the

distribution of the *H. pylori*-induced gastritis.[124-126] The reduction in antisecretory effect would be present but it would be least in patients with antral predominant gastritis, which is associated with unimpaired gastric acid secretion, and greatest in those with corpus gastritis, who have acid secretion impaired by *H. pylori*-induced inflammation and by atrophy, if present. Therefore, inclusion of patients with prior *H. pylori* ulcers may be considered as a source of potential bias that can also potentially erroneously influence the results, resulting in misleading conclusions regarding the safety of a particular anti-inflammatory compound or, conversely, the comparative value of different therapies (e.g. PPIs and misoprostol) in preventing true NSAID-related ulcer.

Another point that is worthy of interest is the adherence to the recommended strategies to reduce the risk of upper GI events. It is well known that PPIs work only when taken; therefore, a strict adherence to gastroprotective treatment is of paramount importance for the success of prevention strategies for GI complications. Several studies[127-129] have suggested that the threshold for effective PPI protection requires that the patients take 80% of the prescribed PPI and that non-adherence to gastroprotective drugs is associated with a 4-fold increased risk of UGIC among high-risk NSAID users, the risk increasing by 16% for every 10% decrease in adherence. Perhaps the issue of compliance may be reduced by the use of a fixed-dose combination of a PPI and NSAID. Clearly, further studies where compliance is directly assessed and studies comparing combination therapy with separately prescribed therapy are needed.

7. Conclusions

In patients receiving NSAID treatment, the prevention and management of related complications must be individualized based on a strategy that balances therapeutic benefits with potential for GI or CV complications.

For patients without CV risk factors, the management plan can be stratified according to the level of GI risk. In the absence of any GI risk factors, patients can be managed with a traditional NSAID. In the presence of GI risk factors, the choice can be made between a traditional NSAID plus a PPI or a coxib, specifically celecoxib. For very high-risk patients, in particular in patients aged >75 years and/or with multiple GI factors or a history of UGIB, the best approach seems to be a coxib plus a PPI, although further studies are required to confirm the relative efficacy of this combined therapy.

The concomitant use of aspirin is an important factor to consider, particularly in older individuals who generally have higher CV risk. While it is clear that coxibs may reduce the risk of GI events, the use of concomitant aspirin is likely to negate the GI benefits of coxibs. Patients with significant CV risk factors requiring prophylactic low-dose aspirin should be treated with an NSAID plus a PPI, regardless of the presence or absence of GI risk factors, as an NSAID plus aspirin already increases the risk of an UGIB to a very significant extent. Finally, any NSAID or coxib should be avoided in patients with very high GI as well as CV risk factors.

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References

1. Tseng C, Wolfe M. Non steroidal antiinflammatory drugs. Med Clin North Am 2000; 84: 1329-44
2. MacDonald TM. Epidemiology and pharmacoeconomic implications of non-steroidal anti-inflammatory drug-associated gastrointestinal toxicity. Rheumatology (Oxford) 2000; 39 Suppl. 2: 13-20
3. Kremer J. From prostaglandin replacement to specific COX-2 inhibition: a critical appraisal. J Rheumatol 2000; 27 Suppl. 60: 9-12
4. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in partients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double blind placebo controlled trial. Ann Intern Med 1995; 123: 241-9
5. Ofman J, Maclean C, Straus WL, et al. A metaanalysis of severe upper gastrointestinal complications of nonsteroidal antiinflammatory drugs. J Rheumatol 2002; 29: 804-12
6. Singh G, Triadafilopoulus G. Epidemiology of NSAID-induced GI complications. J Rheumatol 1999; 26: 18-24
7. Lanas A, Perez-Aisa MA, Feu F, et al. Nationwide study of mortality associated with hospital admission due to severe gastrointestinal events and those associated with non-steroidal

anti-inflammatory drug use. Am J Gastroenterol 2005; 100: 1685-93
8. Cryer B. NSAID-associated death: the rise and fall of NSAID associated GI mortality. Am J Gastroenterol 2005; 100: 1694-5
9. Henry D, McGettigan P. Selective Cox-2 inhibitors: a promise unfulfilled? Gastroenterology 2007; 132: 790-808
10. García Rodríguez LA, Barreales Tolosa L. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. Gastroenterology 2007; 132: 498-506
11. Scheiman JM. Prevention of NSAID-induced ulcers current treatment options. Gastroenterology 2008; 11: 125-34
12. Chen YF, Jobanputra P, Barton P, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess 2008; 12 (11): 1-278
13. Andersohn F, Suissa S, Garbe E. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal anti-inflammatory drugs and risk of acute myocardial infarction. Circulation 2006; 113: 1950-7
14. Howes LG. Selective COX-2 inhibitors, NSAIDs and cardiovascular events: is celecoxib the safest choice? Ther Clin Risk Manag 2007; 3: 831-45
15. Kearney PM, Baigent C, Godwin J, et al. Do selective cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 2006; 332: 1302-8
16. Gabriel SE, Jaakkimainen L, Bomaberdier C. Risk for serious gastrointestinal complications related to use of non-steroidal antiinflammatory drugs: a meta analysis. Ann Intern Med 1991; 115: 787-96
17. Tamblyn R, Berkson L, Duaphinee WD, et al. Unnecessary prescribing of NSAIDs and the management of NSAID-related gastropathy in medical practice. Ann Intern Med 1997; 127: 429-38
18. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007; 66: 377-88
19. Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005; 64: 669-81
20. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000; 343: 1520-8
21. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study. A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000; 284: 1247-55
22. Edwards JE, McQuay HJ, Moore RA. Efficacy and safety of valdecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. Pain 2004; 111: 286-96
23. Hunt RH, Harper S, Watson DJ, et al. The gastrointestinal safety of the COX-2 selective inhibitor etoricoxib assessed by both endoscopy and analysis of upper gastrointestinal events. Am J Gastroenterol 2003; 98: 1725-33
24. Kivitz AJ, Nayiager S, Schimansky T, et al. Reduced incidence of gastroduodenal ulcers associated with lumiracoxib compared with ibuprofen in patients with rheumatoid arthritis. Aliment Pharmacol Ther 2004; 19: 1189-98
25. Laine L, Connors LG, Reicin A, et al. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. Gastroenterology 2003; 124: 288-92
26. Dai C, Stafford RS, Alexander GC. National trends in cyclooxygenase-2 inhibitor use since market release: nonselective diffusion of a selectively cost-effective innovation. Arch Intern Med 2005; 165: 171-7
27. Mamdani M, Juurlink DN, Kopp A, et al. Gastrointestinal bleeding after the introduction of COX 2 inhibitors: ecological study. BMJ 2004; 328: 1415-6
28. Lanas A, Hunt R. Prevention of anti-inflammatory drug-induced gastrointestinal damage: benefits and risks of therapeutic strategies. Ann Med 2006; 38: 415-28
29. Chan FK, Wong VW, Suen BY, et al. Combination of a cyclooxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. Lancet 2007; 369: 1621-6
30. Elliott SL, Ferris RJ, Giraud AS, et al. Indomethacin damage to rat gastric mucosa is markedly dependent on luminal pH. Clin Exp Pharmacol Physiol 1996; 23: 432-4
31. Rowe PH, Starlinger MJ, Kasdon E, et al. Parenteral aspirin and sodium salicylate are equally injurious to the rat gastric mucosa. Gastroenterology 1987; 93: 863-71
32. Shiotani A, Yamaoka Y, El-Zimaity HMT, et al. NSAID gastric ulceration: predictive value of gastric pH, mucosal density of polymorphonucleate leukocytes or levels of IL-8 or nitrite. Dig Dis Sci 2002; 47: 38-43
33. Savarino V, Mela GS, Zentilin P, et al. Effect of one-month treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) on gastric pH of rheumatoid arthritis patients. Dig Dis Sci 1998; 43: 459-63
34. Fledman M, Colturi TJ. Effect of indomethacin on gastric acid and bicarbonate secretions in humans. Gastroenterology 1984; 87: 1339-43
35. Scarpignato C, Pelosini I. Prevention and treatment of non-steroidal anti-inflammatory drug-induced gastro-duodenal damage: rationale for the use of antisecretory compounds. Ital J Gastroenterol Hepatol 1999; 31 Suppl. 1: S63-72
36. Wallace JL, McKnight GW. The mucoid cap over superficial gastric damage in the rat: a high-pH microenvironment dissipated by nonsteroidal antiinflammatory drugs and endothelin. Gastroenterology 1990; 99: 295-304
37. Schmassmann A, Tarnawski A, Peskar BM, et al. Influence of acid and angiogenesis on kinetics of gastric ulcer healing in rats: interaction with indomethacin. Am J Physiol 1995; 268: G276-85
38. Green Jr FW, Kaplan MM, Curtis LE, et al. Effect of acid and pepsin on blood coagulation and platelet aggregation: a possible contributor to prolonged gastroduodenal mucosal hemorrhage. Gastroenterology 1978; 74: 38-43
39. Goldstein JL, Miner Jr PB, Schlesinger PK, et al. Intragastric acid control in non-steroidal anti-inflammatory drug users: comparison of esomeprazole, lansoprazole and pantoprazole. Aliment Pharmacol Ther 2006; 23: 1189-96
40. Blandizzi C, Natale G, Gherardi G, et al. Acid-independent gastroprotective effects of lansoprazole in experimental mucosal injury. Dig Dis Sci 1999; 44: 2039-50

41. Tsuji S, Sun WH, Tsuji M, et al. Lansoprazole induces mucosal protection through gastrin receptor-dependent up-regulation of cyclooxygenase-2 in rats. J Pharmacol Exp Ther 2002; 303: 1301-8
42. Wallace JL, Granger DN. The cellular and molecular basis of gastric mucosal defence. FASEB J 1996; 10: 731-40
43. Suzuki M, Mori M, Miura S, et al. Omeprazole attenuates oxygen-derived free radical production from human neutrophils. Free Radic Biol Med 1996; 21: 727-31
44. Blandizzi C, Fornai M, Colucci R, et al. Lansoprazole prevents experimental gastric injury induced by non-steroidal anti-inflammatory drugs through a reduction of mucosal oxidative damage. World J Gastroenterol 2005; 11: 4052-60
45. Jaworski T, Sarosiek I, Sostarich S, et al. Restorative impact of rabeprazole on gastric mucus and mucin production impairment during naproxen administration: its potential clinical significance. Dig Dis Sci 2005; 50: 357-65
46. Skoczylas T, Sarosiek I, Sostarich S, et al. Significant enhancement of gastric mucin content after rabeprazole administration: its potential clinical significance in acid-related disorders. Dig Dis Sci 2003; 48: 322-8
47. Wiklund I. Quality of life in arthritis patients using non-steroidal anti-inflammatory drugs. Can J Gastroenterol 1999; 13: 129-33
48. Jones RH, Tait CL. Gastrointestinal side-effects of NSAIDs in the community. Br J Clin Pract 1995; 49: 67-70
49. Chan FK, Hung LC, Suen BY, et al. Celecoxib versus diclofenac plus omeprazole in high-risk arthritis patients: results of a randomized double-blind trial. Gastroenterology 2004; 127: 1038-43
50. Bijlsma JW. Treatment of NSAID-induced gastrointestinal lesions with cimetidine: an international multicenter collaborative study. Aliment Pharmacol Ther 1988; 2: 85-95
51. Van Groeneandael JHLM, Markusse HM, Dijkmans BAC, et al. The effect of ranitidine on NSAID-related dyspeptic symptoms with and without peptic ulcer disease of patients with rheumatoid arthritis or osteoarthritis. Clin Rheumatol 1996; 15: 450-6
52. Taha AS, Hudson N, Hawkey CJ, et al. Famotidine for the prevention of gastric an duodenal ulcers caused by non-steroidal antiinflammatory drugs. N Engl J Med 1996; 334: 1435-9
53. Yeomans ND, Tulassay Z, Juhász L, et al. A comparison of omeprazole with ranitidine for ulcers associated with non-steroidal antiinflammatory drugs. Acid Suppression Trial: Ranitidine Versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) Study Group. N Engl J Med 1998; 338: 719-26
54. Hawkey CJ, Karrasch JA, Szczepański 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: 727-34
55. Hawkey C, Talley NJ, Yeomans ND, et al. NASA1 SPACE1 Study Group. Improvements with esomeprazole in patients with upper gastrointestinal symptoms taking non-steroidal antiinflammatory drugs, including selective COX-2 inhibitors. Am J Gastroenterol 2005; 100: 1028-36
56. Hawkey CJ, Jones RH, Yeomans ND, et al. Efficacy of esomeprazole for resolution of symptoms of heartburn and acid regurgitation in continuous users of non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2007; 25: 813-21
57. LoJudice TA, Saleem T, Lang JA. Cimetidine in the treatment of gastric ulcer, induced by steroidal and non-steroidal anti-inflammatory agents. Am J Gastroenterol 1981; 75: 104-10
58. O'Laughlin JC, Silvoso GR, Ivey KJ. Resistance to medical therapy of gastric ulcers in rheumatic disease patients taking aspirin. Dig Dis Sci 1982; 27: 976-80
59. Davies J, Collins AJ, Dixon A. The influence of cimetidine on peptic ulcers patients with arthritis taking anti-inflammatory drugs. Br J Rheumathol 1986; 25: 54-8
60. Roth SH, Bennet RE, Mitchell CS, et al. Cimetidine therapy in non-steroidal antiinflammatory drug gastropathy. Arch Int Med 1987; 147: 1798-801
61. Wallin BA, Frank WO, Fox MJ, et al. The effects of cimetidine on the healing of non-steroidal antiinflammatory drug-induced gastroduodenal damage while continuing NSAID therapy [abstract]. Am J Gastroenterol 1988; 83: 1076
62. Bank S, Zucker S, Grenberg R, et al. Effect of famotidine on gastric ulcer healing: a comparison between nonsteroidal and aspirin induced ulceration and idiopathic ulcers [abstract]. Am J Gastroenterol 1991; 86: 1308
63. Wu CS, Wang SH, Chen PC, et al. Does famotidine have the similar efficacy to misoprostol in the treatment of non-steroidal anti-inflammatory drug-induced gastropathy? Int J Clin Pract 1998; 52: 472-4
64. Lancaster Smith MJ, Jadeberg ME, Jackson DA. Ranitidine in the treatment of non steroidal antiinflammatory drug associated gastric and duodenal ulcer. Gut 1991; 32: 252-5
65. Ehsanullah RS, Page MC, Tildesley G, et al. A placebo-controlled study of ranitidine in healing NSAID-associated gastric and duodenal ulcers [abstract]. Br J Rheumatol 1990; 29 Suppl. 2: 9
66. Misra SP, Kumar N, Anand BS. Aspirin concurrently administered with ranitidine does not delay healing of duodenal ulcer. Aust NZ J Med 1990; 20: 201-3
67. Walan A, Bader JP, Classen M, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. N Engl J Med 1989; 320: 69-75
68. Bianchi Porro G, Lazzaroni M, Manzionna G, et al. Omeprazole and sucralfate in the treatment of NSAID-induced gastric and duodenal ulcer. Aliment Pharmacol Ther 1998; 12: 355-60
69. Agrawal NM, Campbell DR, Safdi MA, et al. Superiority of lansoprazole vs ranitidine in healing nonsteroidal anti-inflammatory drug-associated gastric ulcers: results of a double-blind, randomized, multicenter study. NSAID-Associated Gastric Ulcer Study Group. Arch Intern Med 2000; 160: 1455-61
70. Campbell DR, Haber MM, Sheldon E, et al. Effect of *H. pylori* status on gastric ulcer healing in patients continuing nonsteroidalanti-inflammatory therapy and receiving treatment with lansoprazole or ranitidine. Am J Gastroenterol 2002; 97: 2208-14
71. Olteanu D, Balan C, Andronescu A, et al. Efficacy of pantoprazole as compared to omeprazole and misoprostol in NSAID associated gastric ulcer [abstract]. Gut 2000; 47 Suppl. III: A82
72. Goldstein JL, Johanson JF, Suchower LJ, et al. Healing of gastric ulcers with esomeprazole versus ranitidine in patients who continued to receive NSAID therapy: a randomized trial. Am J Gastroenterol 2005; 100: 2650-7
73. Goldstein JL, Johanson JF, Hawkey CJ, et al. Clinical trial: healing of NSAID-associated gastric ulcers in patients

continuing NSAID therapy. A randomized study comparing ranitidine with esomeprazole. Aliment Pharmacol Ther 2007; 26: 1101-11

74. Laheij RJ, Van Rossum LG, Jansen JB, et al. Proton-pump inhibitor therapy for acetylsalicylic acid associated upper gastrointestinal symptoms: a randomized placebo-controlled trial. Aliment Pharmacol Ther 2003; 18: 109-15
75. Bianchi Porro G, Lazzaroni M, Petrillo M, et al. Prevention of gastroduodenal damage with omeprazole in patients receiving continuous NSAIDs treatment: a double blind placebo controlled study. Ital J Gastroenterol Hepatol 1998; 30: 43-7
76. Daneshmend TK, Stein AG, Bhaskar NK, et al. Abolition by omeprazole of aspirin induced gastric injury in man. Gut 1990; 31: 514-7
77. Scheiman JM, Behler EM, Loeffler KM, et al. Omeprazole ameliorates aspirin-induced gastroduodenal injury. Dig Dis Sci 1994; 39: 97-103
78. Oddsson E, Gudjónsson H, Thjódleifsson B. Comparison between ranitidine and omeprazole for protection against gastroduodenal damage caused by naproxen. Scand J Gastroenterol 1992; 27: 1045-8
79. Simon B, Elsner H, Müller P. Protective effect of omeprazole against low-dose acetylsalicylic acid: endoscopic controlled double-blind study in healthy subjects [in German]. Arzneimittel Forschung 1995; 45: 701-3
80. Labenz J, Blum AL, Bolten WW, et al. Primary prevention of diclofenac associated ulcers and dyspepsia by omeprazole or triple therapy in *Helicobacter pylori* positive patients: a randomised, double blind, placebo controlled, clinical trial. Gut 2002; 51: 329-35
81. Bigard MA. Protective effect of omeprazole on gastric lesions induced by a single dose of aspirin in man. Gastroenterol Clin Biol 1988; 12: 770-1
82. Bergmann JF, Chassany O, Simoneau G, et al. Protection against aspirin-induced gastric lesions by lansoprazole: simultaneous evaluation of functional and morphologic responses. Clin Pharmacol Ther 1992; 52: 413-6
83. Müller P, Fuchs W, Simon B. Studies on the protective effect of lansoprazole on human gastric mucosa against low-dose acetylsalicylic acid: an endoscopic controlled double-blind study [in German]. Arzneimittel Forschung 1997; 47: 758-60
84. Irani S, Krevsky B, Desipio J, et al. Rapid protection of the gastroduodenal mucosa against aspirin-induced damage by rabeprazole. Aliment Pharmacol Ther 2008; 27: 498-503
85. Pilotto A, Di Mario F, Franceschi M, et al. Pantoprazole versus one-week *Helicobacter pylori* eradication therapy for the prevention of acute NSAID-related gastroduodenal damage in elderly subjects. Aliment Pharmacol Ther 2000; 14: 1077-82
86. Pilotto A, Franceschi M, Leandro G, et al. Proton-pump inhibitors reduce the risk of uncomplicated peptic ulcer in elderly either acute or chronic users of aspirin/non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2004; 20: 1091-7
87. Cullen D, Bardhan KD, Eisner M, et al. Primary gastroduodenal prophylaxis with omeprazole for non-steroidal anti-inflammatory drug users. Aliment Pharmacol Ther 1998; 12: 135-40
88. Ekström P, Carling L, Wetterhus S, et al. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous non-steroidal anti-inflammatory drug therapy: a Nordic multicentre study. Scand J Gastroenterol 1996; 31: 753-8
89. Bianchi Porro G, Imbesi V, Lazzaroni M, et al. Efficacy of pantoprazole in the prevention of peptic ulcers induced by nonsteroidal anti-inflammatory drugs: a prospective, placebo-controlled, double-blind: parallel-group study. Dig Liver Dis 2000; 32: 201-8
90. James M, Scheiman MD, Neville D, et al. Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors. Am J Gastroenterol 2006; 101: 701-10
91. Yeomans N, Scheiman JM, Hawkey CJ, et al. An evidence-based analysis of esomeprazole therapy versus placebo for the prevention of gastric or duodenal ulcers in at-risk continous NSAID users [abstract]. Gastroenterology 2004; 126 Suppl. 2: A-604
92. Miyake K, Ueki N, Suzuki K, et al. Preventive therapy for non-steroidal anti-inflammatory drug-induced ulcers in Japanese patients with rheumatoid arthritis: the current situation and a prospective controlled-study of the preventive effects of lansoprazole or famotidine. Aliment Pharmacol Ther 2005; 21 Suppl. 2: 67-72
93. Stupnicki T, Dietrich K, González-Carro P, et al. Efficacy and tolerability of pantoprazole compared with misoprostol for the prevention of NSAID-related gastrointestinal lesions and symptoms in rheumatic patients. Digestion 2003; 68: 198-208
94. Graham DY, Agrawal NM, Campbell DR, et al. NSAID-Associated Gastric Ulcer Prevention Study Group. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. Arch Intern Med 2002; 162: 169-75
95. Rostom A, Wells G, Tugwell P, et al. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database Syst Rev 2000; (4): CD002296
96. Rostom A, Wells G, Tugwell P, et al. Prevention of chronic NSAID induced upper gastrointestinal toxicity. J Rheumatol 2000; 27: 2204-14
97. Leandro G, Pilotto A, Franceschi M, et al. Prevention of severe acute NSAID-related gastroduodenal damage: a meta-analysis of controlled clinical trials. Dig Dis Sci 2001; 46: 1924-36
98. Rostom A, Dube C, Wells G, et al. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database Syst Rev 2002; (4): CD002296
99. Brown TJ, Hooper L, Elliott RA, et al. A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling. Health Technol Assess 2006; 10: 1-183
100. Hooper L, Brown TJ, Elliott R, et al. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. Br Med J 2004; 329: 948-57
101. Chan FK, Chung SC, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose ASA or naproxen. N Engl J Med 2001; 344: 967-73
102. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. N Engl J Med 2002; 346: 2033-8
103. Chan FK, Hung LC, Suen BY, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. N Engl J Med 2002; 347: 2104-10

104. Lai KC, Chu KM, Hui WM, et al. Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications. Am J Med 2005; 118: 1271-8
105. Garcia Rodriguez LA, Ruigomez A. Secondary prevention of upper gastrointestinal bleeding associated with maintenance acid-suppressing treatment in patients with peptic ulcer bleed. Epidemiology 1999; 10: 228-32
106. Fries JF, Murtagh KN, Bennett M, et al. The rise and decline of nonsteroidal antiinflammatory drug-associated gastropathy in rheumatoid arthritis. Arthritis Rheum 2004; 50: 2433-40
107. Lanas A, Rodrigo L, Márquez JL, et al. EMPHASYS Study Group. Low frequency of upper gastrointestinal complications in a cohort of high-risk patients taking low-dose aspirin or NSAIDs and omeprazole. Scand J Gastroenterol 2003; 38: 693-700
108. Ray WA, Chung CP, Stein CM, et al. Risk of peptic ulcer hospitalizations in users of NSAIDs with gastroprotective cotherapy versus coxibs. Gastroenterology 2007; 133: 790-8
109. Rahme E, Barkun AN, Toubouti Y, et al. Do proton-pump inhibitors confer additional gastrointestinal protection in patients given celecoxib? Arthritis Rheum 2007; 57: 748-55
110. Lanas A, Bajador E, Serrano P, et al. Nitrovasodilators, low-dose aspirin, other nonsteroidal anti-inflammatory drugs, and the risk of upper gastrointestinal bleeding. N Engl J Med 2000; 343: 834-9
111. Höer A, Gothe H, Schiffhorst G, et al. Comparison of the effects of diclofenac or other non-steroidal anti-inflammatory drugs (NSAIDs) and diclofenac or other NSAIDs in combination with proton pump inhibitors (PPI) on hospitalisation due to peptic ulcer disease. Pharmacoepidemiol Drug Saf 2007; 16: 854-8
112. Lanas A, García-Rodríguez LA, Arroyo MT, et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. Am J Gastroenterol 2007; 102: 507-15
113. Lanas A, García-Rodríguez LA, Arroyo MT, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut 2006; 55: 1731-8
114. Targownik LE, Metge CJ, Leung S, et al. The relative efficacies of gastroprotective strategies in chronic users of nonsteroidal anti-inflammatory drugs. Gastroenterology 2008; 134: 937-44
115. Hawkey CJ, Lanas AI. Doubt and certainty about nonsteroidal anti-inflammatory drugs in the year 2000: a multidisciplinary expert statement. Am J Med 2001; 110: 79-100S
116. Singh G, Triadafilopoulos G. Appropriate choice of proton pump inhibitor therapy in the prevention and management of NSAID-related gastrointestinal damage. Int J Clin Pract 2005; 59: 1210-7
117. Mel Wilcox C, Allison J, Benzuly K, et al. Consensus development conference on the use of nonsteroidal anti-inflammatory agents, including cyclooxygenase-2 enzyme inhibitors and aspirin. Clin Gastroenterol Hepatol 2006; 4: 1082-9
118. Graham DY. Critical effect of *Helicobacter pylori* infection on the effectiveness of omeprazole for prevention of gastric or duodenal ulcers among chronic NSAID users. Helicobacter 2002; 7: 1-8
119. Chan FKL, Graham DY. Review article: prevention of non-steroidal anti-inflammatory drug gastrointestinal complications. Review and recommendations based on risk assessment. Aliment Pharmacol Ther 2004; 19: 1051-61
120. Graham DY. Ulcer complications and their nonoperative treatment. In: Sleisenger MH, Fordtran JS, editors. Gastrointestinal disease: pathophysiology, diagnosis, management. 5th ed. Philadelphia (PA): WB Saunders Co, 1993: 698-712
121. Graham DY, Lew GM, Klein PD, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer: a randomized, controlled study. Ann Intern Med 1992; 116: 705-8
122. Graham DY, Hepps KS, Ramirez FC, et al. Treatment of *H. pylori* reduces the rate of rebleeding in complicated peptic ulcer disease. Scand J Gastroenterol 1993; 28: 939-42
123. Labenz J, Borsch G. Role of *Helicobacter pylori* eradication in the prevention of peptic ulcer bleeding relapse. Digestion 1994; 55: 19-23
124. Gutierrez O, Melo M, Segura AM, et al. Cure of *Helicobacter pylori* infection improves gastric acid secretion in patients with corpus gastritis. Scand J Gastroenterol 1997; 32: 664-8
125. El-Omar EM, Oien K, El-Nujumi A, et al. *Helicobacter pylori* infection and chronic gastric acid hyposecretion. Gastroenterology 1997; 113: 15-24
126. Labenz J, Tillenburg B, Peitz U, et al. *Helicobacter pylori* augments the pH-increasing effect of omeprazole in patients with duodenal ulcer. Gastroenterology 1996; 110: 725-32
127. Goldstein JL, Howard KB, Walton SM, et al. Impact of adherence to concomitant gastroprotective therapy on nonsteroidal-related gastroduodenal ulcer complications. Clin Gastroenterol Hepatol 2006; 11: 1337-45
128. Van Soest EM, Sturkenboom MC, Dieleman JP, et al. Adherence to gastroprotection and the risk of NSAID-related upper gastrointestinal ulcers and haemorrhage. Aliment Pharmacol Ther 2007; 26: 265-75
129. Abraham NS, Hartman C, Castillo D, et al. Effectiveness of national provider prescription of PPI gastroprotection among elderly NSAID users. Am J Gastroenterol 2008; 103: 323-32

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