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Prevention of upper gastrointestinal haemorrhage: current controversies and clinical guidance

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Abstract: Acute upper gastrointestinal (GI) bleeding is a common medical emergency and associated with significant morbidly and mortality. The risk of bleeding from peptic ulceration and oesophagogastric varices can be reduced by appropriate primary and secondary preventative strategies. *Helicobacter pylori* eradication and risk stratification with appropriate gastroprotection strategies when used with antiplatelet drugs and nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in preventing peptic ulcer bleeding, whilst endoscopic screening and either nonselective beta blockade or endoscopic variceal ligation are effective at reducing the risk of variceal haemorrhage. For secondary prevention of variceal haemorrhage, the combination of beta blockade and endoscopic variceal ligation is more effective. Recent data on the possible interactions of aspirin and NSAIDs, clopidogrel and proton pump inhibitors (PPIs), and the increased risk of cardiovascular adverse events associated with all nonaspirin cyclo-oxygenase (COX) inhibitors have increased the complexity of choices for preventing peptic ulcer bleeding. Such choices should consider both the GI and cardiovascular risk profiles. In patients with a moderately increased risk of GI bleeding, a NSAID plus a PPI or a COX-2 selective agent alone appear equivalent but for those at highest risk of bleeding (especially those with previous ulcer or haemorrhage) the COX-2 inhibitor plus PPI combination is superior. However naproxen seems the safest NSAID for those at increased cardiovascular risk. Clopidogrel is associated with a significant risk of GI haemorrhage and the most recent data concerning the potential clinical interaction of clopidogrel and PPIs are reassuring. In clopidogrel-treated patients at highest risk of GI bleeding, some form of GI prevention is indicated.

Keywords: cyclooxygenase, gastrointestinal haemorrhage, *Helicobacter pylori*, nonsteroidal anti-inflammatory agents, oesophageal and gastric varices, peptic ulcer

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Introduction

Acute upper gastrointestinal bleeding (AUGIB) is a common reason for emergency admission to hospital. In the United Kingdom the rate of admission for nonvariceal upper gastrointestinal (GI) haemorrhage is about 85/100,000 per year and for variceal haemorrhage approximately 2.8/100,000 [Crooks *et al.* 2012]. There appears to be a sociodemographic gradient and the rates of both variceal and nonvariceal haemorrhage are at least doubled in the most socially deprived areas [Crooks *et al.* 2012]. Peptic ulcer bleeding continues to be most common cause of presentation with AUGIB, accounting for about 35% of cases; the incidence of variceal haemorrhage seems to be increasing, particularly in younger patients and, in the recent UK-wide audit, variceal bleeding accounted for 11% of cases [Hearnshaw *et al.* 2011]. Mortality from peptic ulcer (8.9%) and variceal haemorrhage (15%) remains substantial [Hearnshaw *et al.* 2011]. There are excellent guidelines available concentrating on the acute management of AUGIB [Barkun *et al.* 2010]. However because the risk factors and antecedents of AUGIB are often well known, there are potentially several points in the chronic management of these patients where therapeutic interventions can be targeted to reduce the risk of

bleeding. These can take the form of either primary prevention (preventing the first bleeding episode) or secondary prevention (preventing subsequent episodes after a bleeding event). In this review we have concentrated on ways to reduce the risk of, or prevent, AUGIB.

Peptic ulcer bleeding

The main modifiable risk factors for peptic ulcer bleeding are active *Helicobacter pylori* infection and the use of concurrent medications particularly cyclo-oxygenase (COX) inhibitors and antiplatelet agents.

Helicobacter pylori

It is well established that *H. pylori* causes both complicated and uncomplicated duodenal and gastric ulcers and that successful eradication of the organism alters the natural history of the disease and prevents ulcer recurrence [Malfertheiner *et al.* 2012]. Although the prevalence of *H. pylori* infection is possibly slightly lower in bleeding ulcers compared with uncomplicated ulcers, it is also clear that removal of the infection after a peptic ulcer bleed (PUB) episode prevents rebleeding. Rebleeding remains a significant risk in the continued presence of *H. pylori*, but eradication essentially abolishes this risk. A meta-analysis showed that, with successful eradication, the rebleeding rate was 0.22% per year [Gisbert *et al.* 2007], such that continued anti-ulcer therapy is not required in the absence of other risk factors.

Although the absolute rate of PUB after detection of an uncomplicated ulcer is low, again successful eradication prevents bleeding [Sonnenberg *et al.* 1999]. Thus *H. pylori* eradication provides an excellent intervention for primary and particularly secondary prevention of PUB. The exact antibiotic regimens used should be determined by local results and resistance patterns; in the United Kingdom (especially where there are low levels of underlying resistance to macrolides) a 7-day course of twice-daily proton pump inhibitor (PPI), amoxicillin and clarithromycin remains very effective, although in other regions 10- or 14-day regimens are indicated [Malfertheiner *et al.* 2012]. The recent Maastricht consensus guidelines provide excellent guidance on the suitable antibiotic choices [Malfertheiner *et al.* 2012]. Because eradication of the organism so effectively reduces rebleeding, multiple courses of antibiotic therapies, guided if necessary by antibiotic sensitivity data, should be employed to clear the organism.

The interaction of *H. pylori* with other risk factors is not as clear as might have been expected. In general, *H. pylori* infection and aspirin or non-steroidal anti-inflammatory agents (NSAIDs) have independent and additive effects in increasing PUB [Huang *et al.* 2002; Malfertheiner *et al.* 2012]. In some patients, however, those who develop hypochlorhydria in response to *H. pylori* infection may be protective against ulceration [Iijima *et al.* 2012] and further complexity is added as the beneficial effect of acid suppression with PPIs may be enhanced by current *H. pylori* infection [Malfertheiner *et al.* 2012]. In clinical practice it is not usually feasible to detect into which group any one patient falls and *H. pylori* is generally regarded as increasing the overall risk associated with taking aspirin or NSAIDs, and so eradication is always advised.

After an aspirin-induced PUB, in initially infected patients *H. pylori* eradication reduces rebleeding when aspirin is reintroduced (rebleeding rates at 6 months were 1.9% for *H. pylori* eradication alone and 0.9% for maintenance omeprazole alone [Chan *et al.* 2001]). Similarly Chan and colleagues [Chan *et al.* 2013] have also recently reported rebleeding rates after the reintroduction of low-dose aspirin to be lower in those who had had *H. pylori* infection and eradication (0.97% per year) than those that were never infected but had an aspirin-induced GI bleed (5.22% per year). For comparison it should be noted that the bleeding rate in a control group of new aspirin users without any ulcer history was 0.66% per year and that none of the participants were prescribed antisecretory therapy. After an aspirin-induced AUGIB, the rebleeding rate after aspirin reintroduction following *H. pylori* eradication and with lansoprazole coprescription was 1.6% per year compared with 14.8% with eradication therapy alone [Lai *et al.* 2002]. So although *H. pylori* eradication is of benefit after an aspirin-induced AUGIB bleed, the protection is less than that seen with the combination of eradication and maintenance PPI therapy. Therefore eradication should be regarded as one essential element of secondary prevention in this situation.

H. pylori eradication before starting long-term antiplatelet therapy is recommended, as this reduced ulceration but has not been definitively shown to reduce bleeding [Malfertheiner *et al.* 2012].

The situation regarding NSAIDs is even more complex. Eradication before starting NSAIDs is also recommended [Malfertheiner *et al.* 2012], this reduces but does not abolish NSAID-induced peptic ulcers (from 26% to 3% at 8 weeks and 34% to 12% at 6 months [Chan *et al.* 1997, 2002]) but once NSAIDs have been introduced there appears to be some mucosal adaptation and *H. pylori* eradication at that point in patients without ulcers may not offer significant protection [Vergara *et al.* 2005]. After a NSAID-induced PUB, *H. pylori* eradication is inferior to maintenance omeprazole in reducing rebleeding if NSAIDs are restarted (18.8% rebleeding at 6 months compared with 4.4% [Chan *et al.* 2001]). Following a PUB, however, removal of all the different risk factors seems appropriate and *H. pylori* eradication is appropriate but is not a substitute for appropriate pharmacological secondary prevention.

It is important to appreciate that most diagnostic tests for *H. pylori* perform less well in the situation of acute peptic ulcer bleeding. This may be due to blood in the stomach or other factors but the exact reasons remain unclear. The biopsy-based tests (urease, culture and histopathology) all have significantly diminished sensitivity in acute bleeding (sensitivities about 45–70%); faecal antigen testing sensitivity is also reduced, although less so (sensitivity remains at about 87%). Serology remains sensitive, although it is by nature less specific for active infection [Gisbert and Abraira, 2006]. Urea breath testing appears to remains effective in the acute bleeding setting but can be logistically difficult to arrange [Gisbert and Abraira, 2006]. For these reasons the most recent Maastricht guidelines advocate empirical anti *H. pylori* therapy as soon as possible after PUB [Malfertheiner *et al.* 2012]. This strategy is particularly of benefit in areas with a high prevalence of *H. pylori*. This has the advantages of maximizing early eradication and probably reducing loses to follow-up diagnostic testing. However, this does leave the dilemma of what to do after a negative follow-up test: has the infection been cleared or was the patient never infected in the first place? These situations require different management. The authors' preference is for the alternative strategy, as outlined in the Maastricht guidelines, particularly appropriate for low prevalence *H. pylori* areas, that is, performing diagnostic *H. pylori* testing at the initial endoscopy and providing eradication if the tests are positive. If tests are negative, performing a highly specific and sensitive test (either faecal antigen or urea breath test) 6–8 weeks after the acute episode after stopping any PPI therapy and then managing appropriately.

COX inhibitors

It is well established that COX inhibitors increase the risk of peptic ulcer bleeding. Overall most standard nonspecific NSAIDs (nsNSAIDs) increase the risk about 2–4-fold; bleeding rates are approximately 0.2–1.9% per year [Scheiman and Hindley, 2010; Garcia Rodriguez and Barreales Tolosa, 2007]. The basic paradigm underlying the gastroduodenal toxicity of COX-inhibitors is the 'COX-1 hypothesis'. The beneficial effects of COX inhibitors in reducing pain and inflammation are due in inhibition of the COX-2 inducible enzyme isoform, thus reducing the formation of prostaglandins and prostacyclin that contribute to these pathophysiological effects. The other isoform COX-1 is a constitutive ('housekeeping') enzyme expressed in many tissues, including the GI mucosa, where the produced prostaglandins contribute to the continued health of the mucosa by regulating various functions including blood flow and mucus secretion that contribute to 'mucosal defence'. Thus nsNSAIDs that inhibit both isoforms impair mucosal defence and lead to ulceration. This paradigm is supported by clinical studies that show that selective (sCOX-2) inhibitors are as effective as nsNSAIDs for pain and inflammation [Chen *et al.* 2008] and that GI toxicity is generally inversely correlated with COX-2 selectively [Warner *et al.* 1999; Chang *et al.* 2011; Castellsague *et al.* 2009; Garcia Rodriguez, 1997]. However, GI toxicity and bleeding almost certainly have several other determinants including the half-life of the drugs (damage increases with half-life), effects on platelet function and the fact that COX-2 appears to be important in for ulcer healing [Peskar, 2001; Chatterjee *et al.* 2012; Garcia Rodriguez and Barreales Tolosa, 2007]. There are also experimental data showing that inhibition of both COX-1 and COX-2, but not one in isolation, are required to induce peptic ulceration [Wallace *et al.* 2000]. Nevertheless, this model does provide a basis for developing strategies for prevention of PUB in COX inhibitor users.

Preventative strategies

The available strategies, which are not mutually exclusive are: (1) reduce gastroduodenal damage by coprescription of an acid suppressive agent; (2) reintroduce the 'missing' mucosal prostaglandins by using the prostaglandin analogue misoprostol;

and (3) use COX inhibitors that more selectively inhibit COX-2. Of these, misoprostol is rarely used (in the MEDAL programme of COX inhibitor users, only 0.07% used misoprostol compared with over 50% using acid suppression [Laine *et al.* 2007]). Although misoprostol has the advantage of high quality clinical trial data showing that it reduces peptic ulcer complications in NSAID users [Silverstein *et al.* 1995] (and not just surrogate endoscopic or uncomplicated ulcer endpoints), the side effect profile (over 20% get significant diarrhoea) and requirement for multiple daily dosing probably limit its wider use [Targownik *et al.* 2008]. However, misoprostol is available as combined preparation with several NSAIDs and may have a role in certain patients.

By relatively sparing mucosal COX-1, the sCOX-2 agents have a lower incidence of gastrodudoenal ulceration and GI bleeding. Although the sCOX-2 agents usually go under the umbrella of '-coxibs', this belies the complexity of the situation as some traditional nsNSAIDs are relatively COX-2 specific (meloxicam, etodolac and nalbumetone) [Warner *et al.* 1999; Abraham *et al.* 2007]. Even within the coxibs there is a spread of COX-2 selectivity, the now withdrawn rofecoxib and valdecoxib being significantly more selective than the still available celecoxob and etoricoxib [Warner *et al.* 1999]. For the purpose of the prevention of PUB, the authors regard the latter two agents as clinically sCOX-2.

The greater acid suppression produced by PPIs provides greater protection against NSAID-induced ulcers than that seen with standard doses of H2 receptor antagonists (H2RAs) [Lin *et al.* 2011; Lanas *et al.* 2007b]. Although double-dose H2RAs have greater protective effects than standard doses [Targownik *et al.* 2008; Rostom *et al.* 2009], it is difficult to see how this is any advantage over single dose PPI. PPIs prevent NSAID-induced ulceration in endoscopic and clinical studies and large case-control studies have confirmed that PPI coprescription reduces the risk of peptic ulcer bleeding by 50–80% and that this effective reduction is seen against all combinations of risk factors [Lin *et al.* 2011; Lanas *et al.* 2007b]. Data from case-control studies suggest that PPI or sCOX-2 based strategies may be more effective that misopostol-based strategies [Targownik *et al.* 2008]. Particularly now that generic PPIs are available, the simplest strategy to prevent NSAID-induced PUB would be coprescription of PPI with all COX-inhibitors. Economic modelling suggests that this is a cost-effective strategy (Latimer *et al.* 2009) and indeed the United Kingdom National Institute of Clinical Excellence (NICE) has recommended PPI coprescription with all long-term use of NSAIDs or sCOX-2 agents [NICE, 2008]. Despite the long-standing realization that NSAIDs cause PUB, it seems preventative strategies are underused [Lanas *et al.* 2011] and a blanket policy should have the advantage of increasing appropriate use of gastroprotection. Several fixed-dose combinations of NSAIDs and PPIs are now available which may improve concordance.

A blanket policy of PPI gastroprotection is not always advised, perhaps due to cost, increased tablet burden or concerns about long-term use of PPIs. In this situation it is possible to perform risk stratification to inform choices regarding preventative strategies.

Risk stratification for the use of COX-inhibitors and preventative strategies

Although there are no universally validated scoring criteria, several factors have consistently been shown to increase the risk of PUB associated with NSAID use. These are outlined in Box 1. Those outlined have the advantage of being biologically plausible and both clinical relevant and easily

Box 1. Risk factor stratification for acute GI haemorrhage in users of COX inhibitors or antiplatelet agents.

Lowest increase in risk

- Age < 65 years
- No other risk factors

Moderate increase in risk

One or two moderate risk factors:

- Age > 65 years
- In combination with another antiplatelet
- In combination with another NSAID
- In combination with oral bisphosphonate
- In combination with serotonin reuptake inhibitor
- In common with systemic corticosteroids

Highest risk

Three or more moderate risk factors **OR any of:**

- Previous acute upper GI haemorrhage
- Previous peptic ulcer
- In combination with anticoagulation

COX, cyclo-oxygenase; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Table 1. Guidance on suitable strategies for reducing acute GI haemorrhage in users of COX inhibitors with regard to cardiovascular risk.

	Baseline cardiovascular risk	Increased cardiovascular risk *$
Lowest increased risk of upper GI haemorrhage	Non-selective NSAID ‡‖ ***or*** COX-2 selective inhibitor §‖	Naproxen ¶
Moderate increased risk of upper GI haemorrhage	COX-2 selective inhibitor §‖ ***or*** non-specific NSAID plus PPI ***or*** nonspecific NSAID plus misoprostol	Naproxen plus PPI ***or*** naproxen plus misoprostol
Highest risk of upper GI haemorrhage	COX-2 selective inhibitor plus PPI	Generally avoid all nonaspirin COX inhibitors, consider risks on a case-by-case basis

Adapted from guidelines and published data on relative risk of GI bleeding and cardiovascular outcomes (see text for references).
*Established cardiovascular disease or calculated to be at high risk.
$Plus cardioprotective aspirin as indicated.
‡Choice of individual NSAID governed by cost and individual tolerance, use lowest dose possible, lower doses of ibuprofen appear to have the lowest risk of GI haemorrhage.
§COX-2 selective agents generally include celecoxib and etoricoxib.
‖United Kingdom NICE guidelines advocate PPI prophylaxis with all long-term NSAID and COX-2 inhibitor use irrespective of underlying GI risk.
¶PPI prophylaxis is indicated for the aspirin and naproxen combination.
COX, cyclo-oxygenase; GI, gastrointestinal; NICE, National Institute of Clinical Excellence; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

measurable. There are alternative but similar stratification strategies but in general, the more risk factors the greater the risk of bleeding [Lanas *et al.* 2011, 2012], although the absolute increase varies between populations and some patient groups (such as rheumatoid arthritis) probably have an independently increased risk of PUB.

Therefore it is possible to determine three general groups at risk of NSAID-associated PUB and implement a strategy as shown in Table 1. In the lowest risk group (younger patients without risk factors), many authorities would suggest that preventative strategies are not mandatory but that the least GI toxic drug in the lowest possible dose should be used where possible. Ibuprofen appears to be associated with a lower risk of PUB, and piroxicam and azapropazone the highest, with the other nsNSAIDS somewhere in the middle, although there is considerable overlap between the risks attributed to each agent [Henry *et al.* 1996; Chang *et al.* 2011; Castellsague *et al.* 2009; Garcia Rodriguez, 1997; Lanas *et al.* 2006].

The group with modestly (but significantly) increased risk of AUGIB encompasses those with one or two additional risk factors. Age *per se* is probably not a risk factor for AUGIB alone but does exacerbate the effects of NSAIDs or other risk factors. Some form of preventative strategy is appropriate for this group and PPI coprescription with a nsNSAID, a sCOX-2 agent alone or additional misoprostol and a nsNSAID are all suitable. The large clinical trials performed for the launch of the sCOX-2 agents showed that these drugs were associated with significantly less uncomplicated ulcers [Bombardier *et al.* 2000; Laine *et al.* 2007; Silverstein *et al.* 2000]. Bleeding ulcers were less common and the studies failed to convincingly show a significant reduction; however, subsequent case-control studies have shown that sCOX-2 agents are associated with lower rates of ulceration and PUB [Rostom *et al.* 2007, 2009; Lanas *et al.* 2007; Garcia Rodriguez and Barreales Tolosa, 2007]. Individual trials and a meta-analysis have shown that the separate 'PPI + nsNSAID' and 'sCOX-2' strategies are equivalent in reducing ulcer complications [Rostom *et al.* 2009; Fosbol *et al.* 2010; Targownik *et al.* 2008; Lanas *et al.* 2007; Chan *et al.* 2002, 2004; Lai *et al.* 2005] and in a case-control study both were suggested to be more effective than misoprostol [Targownik *et al.* 2008]. Hence the choice of strategy in the moderately increased GI bleeding

risk group can be determined by other factors such as costs and presence of reflux symptoms which might necessitate PPI therapy.

Overall, although sCOX-2 agents are safer from the GI point of view, they are not completely risk free. In the colonic adenoma prevention trial, rofecoxib was associated with a PUB rate of 0.23 per 100 patient years (compared with 0.06 for placebo) [Lanas *et al.* 2007a]; however, most of this residual risk is ameliorated by PPI therapy [Lin *et al.* 2011]. In the highest GI risk group, with a previous NSAID-induced PUB, neither a sCOX-2 alone nor a NSAID + PPI appear to offer sufficient protection with 6-month rebleeding rates of 3.7–4.9% for the sCOX-2 celecoxib and 5.6–6.4% for nsNSAID plus PPI [Chan *et al.* 2002, 2004; Lai *et al.* 2005]. In this highest GI risk group, the optimal treatment if a COX-inhibitor is to be continued is the combination of a sCOX-2 and a PPI. In a well-designed randomized trial, rebleeding after NSAID-induced PUB was significantly lower with celecoxib combined with esomprazole (0%) compared with celecoxib alone (8.9%) [Chan *et al.* 2007]. This sCOX-2 plus PPI combination has also been shown to have the lowest risk of PUB in case control studies [Lin *et al.* 2011].

Cardiovascular toxicity of COX inhibitors

The preventative management of PUB was dealt a serious blow by the withdrawal from the market of the effective sCOX-2 agent rofecoxib because of adverse cardiovascular effects (lumaricoxib was withdrawn because of hepatic toxicity and valdecoxib primarily for skin reactions). Whilst a blow to clinical therapeutics, this could be viewed a proof of pharmacological principles. Normally platelets produce thromboxane A2 (TXA2) *via* a COX-1 dependent pathway, which enhances aggregation. This is balanced by endothelial production of prostaglandins, predominantly prostacyclin (PGI2), which inhibits aggregation. Inhibition of platelet COX-1 protects against thrombotic episodes [Beales and Ogunwobi, 2010]. It has generally been thought that COX-2 was predominantly responsible for the production of PGI2 [Grosser *et al.* 2006], it is not surprising that more selective inhibition of COX-2 tips the balance in favour of platelet activation and increases the risk of circulatory events. Additional mechanisms are probably involved in increasing cardiovascular risk with coxibs, including altered renal electrolyte handling, changes in vascular tone and altered myocardial function and apoptosis [Grosser *et al.* 2006]. However although this 'COX-1 platelets/COX-2 endothelium' model seems to explain the clinical observations and effects of sCOX-2, the simplicity of this concept has been challenged principally by the difficulty in detecting physiological expression of COX-2 in the endothelium [Mitchell *et al.* 2006] and the finding that, experimentally, COX-1 seems to the predominant physiological source of circulating PGI2 [Kirkby *et al.* 2012]. Alternative mechanisms, including the specific ability to inhibit vascular COX-1, may underlie the cardiovascular toxicity of NSAIDs [Mitchell *et al.* 2006].

Further studies have shown that all COX-inhibitors (except aspirin) are associated with an increased risk of cardiovascular outcomes [Kearney *et al.* 2006; Abraham *et al.* 2007; Friedewald *et al.* 2010]. The mechanisms include those mentioned above due to COX-2 inhibition but also complex and variable effects on platelet COX-1. Traditional nsNSAIDs are reversible COX-1 inhibitors and do not seem to produce clinically significant platelet inhibition. In addition several nsNSAIDs, particularly ibuprofen, have been shown to impair the antiplatelet action of aspirin by impairing access of aspirin to its binding site on the active site of the enzyme [Awa *et al.* 2012; Catella-Lawson *et al.* 2001]. There are some data suggesting that the cardiovascular toxicity of naproxen is less than that of comparable nsNSAIDs and sCOX-2 agents [McGettigan and Henry, 2011; Jick *et al.* 2006a, 2006b]; this may be explained by naproxen having a longer half-life [Strand, 2007] and producing significant platelet inhibition itself. This has led to naproxen being commonly advocated as the first-line NSAID in patients with a baseline increased risk of cardiovascular disease [Abraham *et al.* 2010]. This is not without controversy as other studies have shown that, although all COX-inhibitors were associated with an increased risk of cardiovascular adverse effects and the risk correlated with COX-2 selectivity (being highest for rofecoxib the most selective agent), naproxen itself was associated with a four-fold increased risk compared with no treatment and this was not significantly lower than other commonly used nsNSAIDs or even the moderately selective sCOX-2 (and the authors included celecoxib in that group) [Abraham *et al.* 2007].

However given the high prevalence and serious sequelae of cardiovascular adverse events, it is essential that this is factored into any strategy to prevent PUB. A suggested plan is outlined in

Table 2. Primary prevention of oesophageal variceal haemorrhage. (Adapted from AASLD guidelines [Garcia-Tsao *et al.* 2007].)

Size of varice	High risk stigmata (Red Wales sign, Child B/C disease	Treatment
Small	No	1–2 yearly OGD. Beta blocker may be used but long-term benefit not established.
Small	Yes	Nonselective beta blocker
Medium/large	Yes	Nonselective beta blocker or EVBL as primary treatment
Medium/large	No	Nonselective beta-blocker. If contra-indicated/ intolerant, consider EVBL

AASLD, American Association for the Study of Liver Diseases; EVBL, endoscopic variceal band ligation; OGD, oesophagogastroduodenoscopy.

Table 2. Patients can be divided into six groups depending on the presence of high cardiovascular risk (usually defined as established cardiovascular disease or a 10% probability of disease after 10 years by standard risk calculators and/or low/intermediate/high risk of PUB (somewhat heterogeneously but most easily defined as in Table 1 and Box 1 to facilitate clinically useful decisions). Those at low risk of cardiovascular and GI events can receive a nsNSAID (additional PPI may not be necessary), those at modestly increased risk of GI toxicity but no increased cardiovascular risk a sCOX-2 (or nsNSAID + PPI, or nsNSAID + misoprostol), and those at highest risk of GI events without increased cardiovascular risk should receive a sCOX-2 plus PPI. Patients at increased cardiovascular risk but intermediate GI risk are probably best treated based on current evidence with naproxen + PPI (plus cardioprotective aspirin as appropriate), whilst those with significant cardiovascular and GI risks should ideally avoid all nonaspirin COX-inhibitors [Abraham *et al.* 2010]. In practice this is a significant group and decisions will need to be based on individual circumstances and perceived risks and benefits, although as discussed below accruing data may inform these decisions.

Interactions between aspirin and COX-2 inhibitors

There are complex and incompletely understood interactions between aspirin and COX inhibitors. As discussed above, probably all nonaspirin COX inhibitors increase the risk of cardiovascular events and the combination of aspirin and a COX inhibitor increases the risk of PUB [Lanas *et al.* 2006, 2012; Lin *et al.* 2011]. As may be expected from pharmacological principles, the addition of the COX-1 inhibitor action of aspirin to a sCOX-2 negates the absolute reduction in GI events seen compared with an nsNSAID alone [Silverstein *et al.* 2000; Rostom *et al.* 2009; Lanas *et al.* 2006], and in view of this and the perceived cardiovascular toxicity of sCOX-2, this combination is generally avoided. At the same time, experimentally several nsNSAIDs and sCOX-2s impair the COX-1 inhibitory action of aspirin and certainly ibuprofen impairs the antiplatelet action *in vivo* [Rimon *et al.* 2010; Awa *et al.* 2012; Catella-Lawson *et al.* 2001]. This effect is seen if the ibuprofen is given prior or up to 1 hour after aspirin but not if aspirin is given 2 hours before ibuprofen [Awa *et al.* 2012]. Noncompetitive binding of ibuprofen within the active site of COX-1, thus preventing aspirin covalently binding to COX-1, is the likely mechanism. Similar detailed interactions have not been explored for all other nsNSAIDs, but when used in combination it may be wise to avoid nsNSAID dosing prior to aspirin.

The two major questions on which clarity is needed to inform choices regarding the clinical use of aspirin combined with NSAIDs concern the relative effects on GI toxicity, and whether the cardioprotective effects of aspirin persist during coprescription of other COX-inhibitors. It does seem that the combination of sCOX-2 plus aspirin is indeed less GI toxic than nsNSAID plus aspirin [Laine *et al.* 2007; Goldstein *et al.* 2006, 2007]. The beneficial cardiovascular effects of aspirin have been found to persist in conjunction with both sCOX-2s and nsNSAIDs, including celecoxib, rofecoxib, indomethacin and meloxicam but not ibuprofen [Strand, 2007]. It may be necessary to consider each drug individually rather than as a class, as

effects may not merely be mediated merely by COX inhibition but involve pharmacokinetics, membrane binding and metabolism [Strand, 2007]. Although it may be too soon to change the overall suggestions outlined previously (Table 2), if further studies are confirmatory, the combination of aspirin + sCOX-2 + PPI may become the optimal treatment strategy for those with cardiovascular disease and high risk of PUB.

Upper GI bleeding with antiplatelet agents

Three classes of antiplatelet agent are in common use: aspirin, dipyridamole and the P2Y12 (ADP-) receptor antagonists exemplified by clopidogrel. Of these, dipyridamole does not seem to be associated with increased risk of AUGIB [Ibanez *et al.* 2006] and, as it is only generally used in combination with aspirin, management decisions are based on the aspirin risk.

Aspirin and clopidogrel inhibit platelet function by separate and complimentary mechanisms, and both are associated with increased risk of AUGIB; the mechanism probably stems from impaired platelet aggregation enhancing bleeding from pre-existing gastric erosions [Abraham *et al.* 2010]. There are data showing that platelet derived factors influence peptic ulcer healing and vascularity and inhibition of this facet of platelet function probably also contributes [Ma *et al.* 2001]. Enteric coated or buffered aspirin preparations do not provide significant protection, suggesting that systemic rather than local effects are most important [Bhatt *et al.* 2008]. Although the COX-1 inhibitory effect of aspirin on the GI mucosa might be expected to cause greater rates of PUB, in practice clopidogrel is not clinically safer from this perspective. Although rates of both total GI haemorrhage (1.99% *versus* 2.66%) and life-threatening GI haemorrhage in the CAPRIE trial were statistically lower in clopidogrel compared with aspirin-treated patients, the difference in rate of major bleeding of 2/1000 per year is not meaningful in determining preventative strategies (CAPRIE Steering Committee, 1996). Similar results have been seen in a large population-based case control study where clopidogrel was associated with the same degree of increased risk as aspirin, anticoagulants or nsNSAIDs (relative risk compared with no treatment of 1.9–4.2) [Lanas *et al.* 2006]. Dual antiplatelet combination is associated with increased risk of PUB. Overall rates of GI bleeding are about 0.6–1.0% per year with aspirin alone and are increased by about approximately a further 1% by the addition of clopidogrel [Lanas *et al.* 2006; Ng *et al.* 2008; Hsu *et al.* 2011; CAPRIE Steering Committee, 1996; Lin *et al.* 2011]. There are less data for other P2Y12 antagonists such as prasugrel or ticagrelor, but given the similar mechanism of action, similar effects are likely. Compared with NSAIDs, the risk factors for bleeding with antiplatelets are less well defined but in practice a similar risk stratification strategy as outlined for NSAIDs in Box 1 is appropriate. It is important to continue cardioprotective aspirin after a PUB in patients with established cardiovascular disease as discontinuation has been reported to be associated with a high rate of death or cardiovascular events in the 6 months after aspirin cessation (31% compared with 8% in those that had aspirin re-introduced) [Derogar *et al.* 2013]. A combined aspirin cardiovascular/GI risk calculator has recently been published based on similar risk assumptions, and although this requires further external validation, this can be used to guide physicians in making decisions about the appropriateness of both aspirin and gastroprotection in various circumstances [Lanas *et al.* 2013].

As the absolute risk of bleeding with a single antiplatelet agent is low, gastroprotection is not usually recommended in the absence of other risk factors [Abraham *et al.* 2010]. Therefore prevention is usually recommended for the over 65s, when combined with other drugs increasing the risk (including another nondipyidamole antiplatelet) or a past history of dyspepsia, peptic ulcer or bleeding.

Coprescription of a PPI with antiplatelet therapy is usually recommended if gastroprotection is indicated [Abraham *et al.* 2010]. High-dose famotidine has also been showed to be effective against aspirin-induced ulceration [Taha *et al.* 2009], but in another randomized trial, pantoprazole was superior to famotidine in prevention of PUB [Ng *et al.* 2010] and case-control studies support the concept that PPI coprescription is more effective than H2RAs [Lanas *et al.* 2007b]. H2RAs have not been specifically examined in randomized trials in relation to clopidogrel-induced AUGIB, although the American College of Cardiology Foundation (ACCF), American College of Gastroenterology and American Heart Association (AHA) consensus guideline suggests that H2RA (but not cimetidine) may be an option for clopidogrel-treated patients with modestly increased bleeding risk [Abraham *et al.* 2010]. In a randomized placebo-controlled trial, after an

aspirin-induced but not necessarily complicated, peptic ulcer clopidogrel alone was associated with an ulcer recurrence rate of 11% at 6 months and esomprazole reduced this to 1.2% [Hsu *et al.* 2011] and in a similar randomized trial after aspirin-induced bleeding ulcer, clopidogrel (13.6% recurrent ulcer complications) was inferior to esomeprazole plus aspirin (0%) [Lai *et al.* 2006]. When looking specifically at ulcer bleeding, in a randomized trial omeprazole reduced upper GI bleeding induced by the aspirin–clopidogrel combination by 87% compared with placebo [Bhatt *et al.* 2010]. There are no studies comparing aspirin plus PPI against clopidogrel plus PPI in the secondary prevention of PUB.

Therefore PPI therapy reduces bleeding associated with antiplatelet drugs [Bhatt *et al.* 2010], but recent studies have questioned whether the combination of PPI and clopidogrel is appropriate. Clopidogrel is a prodrug, which requires biotransformation by the hepatic cytochrome enzyme, CYP2C19, for activity. Certain drugs, including some PPIs, inhibit this enzyme and pharmacodynamic studies have clearly shown that co-administration of PPIs with clopidogrel appeared to impair the antiplatelet action of clopidogrel [Gilard *et al.* 2008]. Initial results from observational studies seemed to indicate that the addition of a PPI was associated with an increased cardiovascular risk in clopidogrel-treated patients. The current guidance from the United Kingdom Medicine and Healthcare Products Regulatory Agency (MHRA) and the United States Federal Drug Administration (FDA) continue to suggest avoiding the addition of omeprazole [FDA 2010] or either omeprazole or esomeprazole [MHRA 2010] to clopidogrel (because these may be associated with greater CYP2C19 inhibition) [MHRA, 2010]. Subsequent studies and meta-analyses have shown that there does not seem to be a clinically significant interaction between PPIs and clopidogrel [Mizia-Stec *et al.* 2012; Focks *et al.* 2013; Kwok and Loke, 2010] and certainly in the highest GI bleeding risk patients the addition of PPI gastroprotection would be appropriate. Although there are limited data in this situation, theoretically pantoprazole would be expected to have the least interaction with clopidogrel [Mizia-Stec *et al.* 2012].

H. pylori, aspirin and NSAID negative ulcers

Peptic ulceration in the absence of the traditional major risk factors is increasing recognized as a significant clinical problem. It is important to consider gastrinoma as a cause of such ulcers, but in practice, this is a rare cause. These idiopathic ulcers are associated with an overall poor prognosis, with a very high incidence of adverse cardiovascular outcomes but also a very high risk of rebleeding (42% at 7 years) [Wong *et al.* 2009]. Continued acid suppression would be recommended as secondary prevention following an AUGIB from an idiopathic ulcer. However, this may not be that effective. Wong and colleagues reported that the continued use of a PPI was not associated with a significantly reduced risk of rebleeding (relative risk 0.7, 95% confidence interval 0.4–1.1) [Wong *et al.* 2012]. It may yet be proved that mucosal protectants such as misoprostol or sucralfate offer an advantage, but at present it still seems sensible to recommend PPI gastroprotection in this group.

Prevention of variceal bleeding

Bleeding from oesophageal or gastric varices is less common than peptic bleeding, accounting for 11% of presentations compared with 36% for peptic ulcer in the recent UK-wide audit [Hearnshaw *et al.* 2011]. However, the mortality of variceal bleeding is significantly higher (15 *versus* 8.9%) and variceal bleeding seems to becoming commoner, particularly in younger age groups (accounting for 20% of new upper GI bleeding presentations in those aged <60) [Hearnshaw *et al.* 2011]. Although the pathogenesis of variceal bleeding differs from peptic ulcer bleeding, because the major antecedents are known there are again several points at which preventative therapies can be utilized.

Variceal bleeding is one of the most important complications of chronic liver disease and portal hypertension. The prevalence of gastro-oesophageal varices ranges from 0–40% in compensated to 70–80% in decompensated disease [Garcia-Tsao *et al.* 2007]. The risk of bleeding varies between 8 and 35% within 2 years of follow up [Drastich *et al.* 2011], with a mortality rate of up to 30–50% with each bleeding episode [Jalan and Hayes, 2000; Li *et al.* 2011]. Variceal bleeding can also trigger other complications of cirrhosis such as encephalopathy, spontaneous bacterial peritonitis and hepatorenal syndrome [Jalan and Hayes, 2000].

Pathophysiology of portal hypertension and varices

Although there are many causes of portal hypertension, in the developed world, cirrhosis remains

the predominant cause due to a variety of causes [Chen and Ghali, 2012] and the majority of published data refer to this situation. Portal hypertension develops as a result of increased vascular resistance due to distorted hepatic architecture in a cirrhotic liver and active intrahepatic vasoconstriction due to a decrease in the endogenous production of nitric oxide [Garcia-Tsao *et al.* 2007] and inappropriate production of vasoconstrictors such as endothelin, angiotensin II and leukotrienes [Lo *et al.* 2004]. The increase in portal pressure results in the formation of collateral circulation to allow portal blood to be diverted into the systemic circulation at the sites of potential portal systemic anastomoses, primarily through the extrinsic and intrinsic gastro-oesophageal veins, the para-umbilical veins, the superior haemorrhoidal vein, and in the abdominal wall and retroperitoneal tissues [Jalan and Hayes, 2000]. Multiple studies have demonstrated that varices develop and enlarge with time especially in the context of ongoing liver injury [Jalan and Hayes, 2000].

Primary prevention

The knowledge that variceal bleeding is related to the pressure in the portal system, and hence within the varices, directs the application of therapies to lower portal pressure and hence prevent the first episode of bleeding. The mainstays of treatment for such primary prevention are currently nonselective beta blockers [Chen and Ghali, 2012]. The aim of this treatment is to reduce portal pressure, with a target portal pressure gradient of less than 12 mmHg, although in practice using the portal pressure gradient to guide therapy (which requires invasive techniques) is not widely used [Jalan and Hayes, 2000; Bureau *et al.* 2002]. Nonselective beta blockers (usually propranolol or nadolol) are preferred as the beta-1 inhibition reduces cardiac output and hence blood flow into the mesenteric system, whilst beta-2 blockade induces splenic vasoconstriction further resulting in decreased portal flow and pressure. In up to 40% of patients, however, the reduction in portal pressure fails to fall below that required to prevent bleeding [Li *et al.* 2011; Drastich *et al.* 2011]. Around one in five patients is unable to tolerate high doses and therefore withdraws from treatment [Lay *et al.* 2006]. The main alternative to beta blockers is endoscopic variceal banding ligation (EVBL). This does not alter the underlying portal haemodynamics but, by inducing thrombosis in oesophageal varices, can lead to eradication of varices and prevention of oesophageal variceal haemorrhage. Although effective, it is associated with serious side effects such as postligation ulceration and bleeding, and requires repeated endoscopic procedures [Funakoshi *et al.* 2012; Lo *et al.* 2008].

There remains controversy as to whether endoscopic band ligation or beta blockers provide better results with regards to primary prophylaxis. A meta-analysis of all studies in 2011 (although limited by a lack of blinding, underpowered studies and varying study design) showed no significant differences in mortality [Li *et al.* 2011]. This may be due to the fact that banding does not treat portal hypertension or the underlying disease process [Bosch and Garcia-Pagan, 2003]. More recently an extensive meta-analysis of 19 eligible reports showed that EVBL is associated with a significant reduction in bleeding rates and a nonsignificant decrease in all-cause mortality [Funakoshi *et al.* 2012]. Although there were more side effects associated with beta blockers, there were more fatal adverse effects with EVBL, predominantly due to banding related ulceration and bleeding.

Recent reports have shown that nonselective beta blockers may contribute to paracentesis-induced circulatory dysfunction in patients with refractory ascites [Serste *et al.* 2011]. As such many hepatology centres now recommend the use of band ligation as primary prevention of variceal bleeding in patients with ascites, whereas beta blockers are commonly used for those without ascites. Band ligation is appropriate primary prevention for those in whom beta blockers are contraindicated (such as asthmatics) or not tolerated.

There is not thought to be a role for transjugular intrahepatic portosystemic (TIPPS) shunts in primary or secondary prevention of oesophageal varices due to an increased risk of encephalopathy and increased mortality, despite being very effective at preventing bleeding [Jalan and Hayes, 2000; Chen and Ghali, 2012].

The development of varices is common in patients with cirrhosis; approximately 50% of cirrhotics have varices [Garcia-Tsao *et al.* 2007]. It is believed that about 8% of patients with cirrhosis develop oesophageal varices each year [Garcia-Tsao *et al.* 2007]. The single most important predictor for the development and progression of oesophageal varices is the severity of the underlying liver disease [Garcia-Tsao *et al.* 2007]. No

pharmacological therapies have been shown to prevent the development of varices [Garcia-Tsao *et al.* 2007]. Despite the high prevalence of oesophageal varices, however, bleeding is relatively uncommon. Around 5–15% of patients with varices will have a significant bleeding episode per year and the most important predictors of future variceal haemorrhage are the size of the varices and the presence of red signs on the varices [Garcia-Tsao *et al.* 2007]. Knowledge of these antecedents of oesophageal variceal bleeding enables the development of a policy of endoscopic screening for varices in cirrhotic patients, with beta blockers or EVBL applied depending on the underlying severity of the liver disease, complications, contraindications and the endoscopic appearance of the varices. The guidelines from the American Association for the Study of Liver Disease (AASLD) are summarized in Table 2 [Garcia-Tsao *et al.* 2007].

The British Society of Gastroenterology guidelines [Jalan and Hayes, 2000] recommend primary prophylaxis for all grade 3 varices (occluding lumen) irrespective of the underlying severity of the liver disease and for grade 2 (moderate) varices with Child's B and C grade liver disease. Propranolol is the treatment of choice with a starting dose of 40 mg twice daily increasing to 80 mg twice daily if necessary. The AASLD guidelines suggest increasing the beta blocker dose to the maximum clinically tolerated [Garcia-Tsao *et al.* 2007].

Secondary prevention

Having an oesophageal variceal haemorrhage is a major risk factor for subsequent bleeding. Patients surviving a variceal bleed have a rebleeding risk of 60% in the first year [Bosch and Garcia-Pagan, 2003] and a mortality of 33% [Chen and Ghali, 2012]. Hence, secondary prevention is appropriate in this situation.

Beta blockade with propranolol or nadolol has been shown to significantly reduce rebleeding and mortality [Jalan and Hayes, 2000]. It has been reported that the combination of oral isorbide mononitrate and nadalol provides a survival advantage compared with repeat banding in secondary prevention, despite being significantly less effective at preventing rebleeding [Lo *et al.* 2008]. This may be due to beta blockers attenuating the other complications of portal hypertension as well as reducing the risk of variceal haemorrhage [Lo *et al.* 2004]. The addition of nitrates has been shown to aid in achievement of target hepatic venous pressure gradients with a resultant significant reduction in variceal bleeding (10% *versus* 64% in nonresponders) [Bureau *et al.* 2002]. Nitrates, however, are not recommended in primary prophylaxis [Al-Busafi *et al.* 2012]. There are similar rebleeding risks at 1 year between combination drug therapy (44%) and banding (54%), and the combination of band ligation and medical therapy results in a reduced rebleeding rate [Thiele *et al.* 2012]. The current recommendations are for combination therapy (endosopic and pharmacological) to be started as soon as possible after initial bleeding episode [Chen and Ghali, 2012; Thiele *et al.* 2012].

British Society of Gastroenterology currently recommends eradication of varices with banding the preferred method for secondary prevention [Jalan and Hayes, 2000]. If beta blockers are used as monotherapy then it is recommended patients have the hepatic venous pressure gradient measured to confirm it has been reduced below 12 mmHg. AASLD guidelines published in 2007 agree that all survivors of variceal bleeds should receive secondary prophylaxis and recommend combination therapy with nonselective beta blocker and ligation banding [Garcia-Tsao *et al.* 2007]. Endoscopic sclerotherapy is no longer recommended as it has been shown that EVBL is superior in regards to rebleeding rates, mortality and the development of strictures [Al-Busafi *et al.* 2012].

Gastric varices

Gastric varices occur in around 20% of patients with portal hypertension [Sarin and Lahoti, 1992]. They are normally identified at a time of bleeding and are associated with a more severe haemorrhage, require more transfusion and have a higher mortality than oesophageal bleeding [Kang *et al.* 2011; Sarin and Lahoti, 1992].

Compared with oesophageal varices, there are few data regarding primary prevention of gastric variceal bleeding. It has been shown that injection of high risk gastric varices (advanced Child–Pugh stage, presence of red spots and increasing size of varices) with *N*-butyl-2-cyanoacrylate had a favourable outcome as primary prevention with a 75% 1-year survival rate, no bleeding episodes and no complications [Kang *et al.* 2011]. Beta blockers are more effective than no treatment in

primary prophylaxis, but less effective than cyanoacrylate injection [Mishra *et al.* 2011]. The threshold for inserting a transjugular intrahepatic portal systemic shunt (TIPS) is lower in the treatment of gastric compared with oesophageal variceal haemorrhage. Although not specifically indicated in the elective secondary prevention of gastric variceal haemorrhage, the early use of TIPS as rescue therapy after failed endoscopic therapy provides both control of acute bleeding and effective secondary prevention [Chau *et al.* 1998; Garcia-Tsao *et al.* 2007].

Conclusion

Acute upper GI haemorrhage remains a common medical emergency associated with significant morbidity and mortality. Haemorrhage from peptic ulceration or oesophagogastric varices are the major causes and an understanding of the risk factors enables appropriate strategies for primary and secondary prevention to be utilized. Certainly for peptic ulcer bleeding, preventative strategies appear to be used suboptimally. The main modifiable risk factors for peptic ulcer bleeding are *H. pylori* infection, and the use of NSAIDs and antiplatelet agents. Eradication of *H. pylori* is a very effective secondary prevention strategy but the limitations of the available tests in the peribleeding period need to be considered. *H. pylori* eradication before starting NSAIDs or aspirin is also indicated to reduce the risk of subsequent bleeding. However this is in addition to, and not a substitute for, careful risk assessment and the use of gastroprotection strategies (usually with a proton pump inhibitor) and/or the use of a selective COX-2 inhibitor.

Recent publications on the cardiovascular risk associated with NSAIDs and COX-2 inhibitors, the possible interactions of aspirin and NSAIDs and clopidogrel with PPIs have added considerably to the complexity of preventing GI bleeding and have emphasized the importance of considering the risks of circulatory diseases as well as GI bleeding. A blanket policy of PPI coprescription with all NSAIDs and COX-2 inhibitors may be cost effective, but this may not necessary for those with no other risk factors for GI bleeding. In patients at moderately increased risk of bleeding either a nsNSAID or a COX-2 inhibitor alone appear equivalent, but the COX-2 inhibitor plus PPI combination is recommended for those at highest risk of bleeding. All nonaspirin COX inhibitors appear to be associated with an increased risk of cardiovascular events and, at present, naproxen (with a PPI) appears to be the safest choice if patients with increased cardiovascular risk require an anti-inflammatory agent. Preventative strategies in those at highest risk of both GI bleeding and cardiovascular events need to be individualized pending further data.

Both aspirin and clopidogrel alone are associated with increased and similar rates of GI haemorrhage, clopidogrel in practice is not markedly safer than aspirin, and aspirin plus a PPI, and not clopidogrel is preferred after an aspirin-induced GI haemorrhage. The optimal GI preventative strategy when clopidogrel is definitely indicated remains unclear, although the most recent data suggest that PPIs can be used safely and effectively with clopidogrel. In patients with the highest risk of GI bleeding on dual antiplatelet therapy, pantoprazole seems the optimal choice based on presently available data.

Primary prevention of oesophageal variceal haemorrhage relies on endoscopic screening for varices, and subsequently either nonselective beta blockade or endoscopic variceal ligation; both reduce the risk of haemorrhage. In secondary prevention after an oesophageal variceal haemorrhage, the combination of beta blockers and endoscopic therapy is preferred.

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