Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding

Joseph J Y Sung,[1] Francis K L Chan,[2] Minhu Chen,[3] Jessica Y L Ching,[3] K Y Ho,[4] Udom Kachintorn,[3] Nayoung Kim,[5] James Y W Lau,[3] Jayaram Menon,[3] Abdul Aziz Rani,[3] Nageshwar Reddy,[3] Jose Sollano,[6] Kentaro Sugano,[7] Kelvin K F Tsoi,[2] Chun Ying Wu,[3] Neville Yeomans,[3] Namish Vakil,[8] K L Goh[3]

[1]Institute of Digestive Disease, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong
[2]Department of Medicine & Therapeutics, Asia-Pacific Working Group, Shatin, Hong Kong
[3]Asia-Pacific Working Group, China
[4]Department of Medicine, Asia-Pacific Working Group, National University Hospital, Singapore
[5]Asia-Pacific Working Group, Korea
[6]Asia-Pacific Working Group, Philippines
[7]Asia-Pacific Working Group, Japan
[8]Aurora Summit Medical Center, University of Wisconsin, Summit, USA

Correspondence to
Joseph Sung, Institute of Digestive Disease, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong; joesung@cuhk.edu.hk

ABSTRACT

Upper gastrointestinal bleeding (UGIB), especially peptic ulcer bleeding, remains one of the most important cause of hospitalisation and mortality world wide. In Asia, with a high prevalence of *Helicobacter pylori* infection, a potential difference in drug metabolism, and a difference in clinical management of UGIB due to variable socioeconomic environments, it is considered necessary to re-examine the International Consensus of Non-variceal Upper Gastrointestinal Bleeding with emphasis on data generated from the region. The working group, which comprised experts from 12 countries from Asia, recommended the use of the Blatchford score for selection of patients who require endoscopic intervention and which would allow early discharge of patients at low risk. Patients' comorbid conditions should be included in risk assessment. A pre-endoscopy proton pump inhibitor (PPI) is recommended as a stop-gap treatment when endoscopy within 24 h is not available. An adherent clot on a peptic ulcer should be treated with endoscopy combined with a PPI if the clot cannot be removed. Routine repeated endoscopy is not recommended. High-dose intravenous and oral PPIs are recommended but low-dose intravenous PPIs should be avoided. COX-2 selective non-steroidal anti-inflammatory drugs combined with a PPI are recommended for patients with very high risk of UGIB. Aspirin should be resumed soon after stabilisation and clopidogrel alone is no safer than aspirin plus a PPI. When dual antiplatelet agents are used, prophylactic use of a PPI reduces the risk of adverse gastrointestinal events.

BACKGROUND

Although there is a general declining trend in the incidence of peptic ulcer disease, non-variceal upper gastrointestinal bleeding (NVUGIB) remains a major prevalent and clinically significant condition world wide. Recent studies suggest that the incidence of NVUGIB ranges from 20 to 60 per 100 000 population in North America and in Europe,[1-3] with an increasing elderly population with comorbid illness.

The International Consensus Recommendations on the Management of Patients with Non-variceal Upper Gastrointestinal Bleeding (ICON-UGIB) published in 2010 was a collective wisdom of 34 voters from 15 countries.[1] It takes into account the updated literature on the management of NVUGIB

Significance of this study

What is already known about this subject?
► Both Blatchford and Rockall scores are suitable for predicting the need for endoscopic intervention in upper gastrointestinal bleeding (UGIB).
► Endoscopic intervention within 24 h of onset of bleeding improves outcomes in patients at high risk.
► High-dose intravenous proton pump inhibitors (PPIs) are effective in reducing rebleeding from peptic ulcer disease.
► PPIs may interact with clopidogrel leading to a reduction in antiplatelet activity.

What are the new findings?
► To assess the need for endoscopic intervention in Asian patients with UGIB, the Blatchford score is preferred.
► When an emergency endoscopy service is available over weekends and public holidays, no increased mortality is seen at these times.
► High-dose oral PPIs may be effective in reducing rebleeding in Asian patients.
► Among patients receiving clopidogrel and aspirin as dual treatment, prophylactic use of a PPI is still recommended to reduce the risk of adverse gastrointestinal (GI) events.

How might it impact on clinical practice in the foreseeable future?
► Endoscopy should be made available in all practices to provide the service within 24 h of presentation of upper GI bleeding.
► When indicated, dual antiplatelet treatment should be prescribed with PPIs in patients who are at high risk for GI bleeding.

and draws up consensus guidelines based on the modified Delphi process. It has five sections—namely, 1. resuscitation, risk assessment and pre-endoscopy management; 2. endoscopic management; 3. pharmacological management; 4. non-pharmacological and non-endoscopic in-hospital management; 5. postdischarge management, including the use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). Although the guidelines present comprehensive recommendations and the latest update of the literature, they do not

allow for the specific needs of resource-limited countries and differences due to ethnicity. For example, the use of pre-endoscopic proton pump inhibitor (PPI) treatment to down-stage endoscopic lesions and decrease the need for endoscopic intervention is considered in the ICON-UGIB. This causes financial burden to resource-limited countries in the Asia-Pacific region. High-dose infusion of a PPI is recommended as an adjuvant to endoscopic treatment but, after considering all the studies available, the ICON-UGIB did not reach a conclusion about the efficacy of either lower intravenous doses or high-dose oral PPI treatment. Furthermore, there are regional differences in *Helicobacter pylori* infection, metabolism of drugs such as PPIs and antiplatelet agents, which may have implications for the management of NVUGIB.

The Asia-Pacific Working Group of Upper Gastrointestinal Bleeding was a collection of gastroenterologists and surgeons who are in active clinical practice and research in gastroenterology. They came from 12 countries/regions—namely, Australia, China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan and Thailand. The aim of revising the management guidelines for UGIB is to consider the regional differences in patient characteristics and healthcare system. Whenever possible, Asian data were used to form the basis of the consensus statement. These guidelines are not meant to cover every detail in the management of NVUGIB. Instead, they highlight the important strategies that may be more suitable for use in the Asia-Pacific Region. The consensus meeting was convened in Bangkok in March 2010.

METHODS
Literature searches included Medline, Embase, the Cochrane Central Register of Controlled Trials and ISI Web of Knowledge with manual searches of bibliographies of key articles and proceedings of abstracts of major gastroenterology meetings held in the past 5 years (Asian Pacific Digestive Week (APDW), Digestive Disease Week, United European Gastroenterology Week). Key words used include gastrointestinal bleeding, peptic ulcer disease and Asia. Studies from Asia were discussed in detail for their strengths and weaknesses. The specific features of these studies in relation to regional differences were emphasised.

Working group members who came from the 12 countries/ regions mentioned above were selected from the scientific committee of the APDW 2010 for their expertise in areas of acute UGIB, evidence-based medicine and continuing medical education and representation of their own country/region. The preparation committee in this working group, which comprised Joseph Sung, KL Goh, Francis Chan and James Lau, identified statements to be discussed. Based on the modified Delphi process, the draft statements were sent to all members of the Asia-Pacific working group, together with evidence-based reviews and other pertinent literature. A first round of voting on the statements was conducted by email. Each statement was assessed on a five-point Likert scale: 1. accept completely; 2. accept with some reservation; 3. accept with major reservation; 4. reject with reservation; 5. reject completely. Results and comments were collated. Agreement with a statement by 80% of the working group (ie, the proportion of the working group answering 1 plus those answering 2 was ≥80%) was defined a priori as consensus. Based on first-round voting comments, modifications were made to the statements by a steering committee comprising Joseph Sung, KL Goh, Udom Kachintorn, Francis Chan, James Lau, Nageshwar Reddy, Neville Yeomans and Namish Vakil. These modified statements were discussed during the meeting, followed by a second round of voting with

electronic keypads, until consensus was reached on all statements. Participants voted anonymously on statements after discussion and provided comments on the wording of the statements, which were progressively finalised through two separate iterations during the 2-day meeting. If there was still no consensus—that is, agreement was <80%, the statement was rejected. Members also discussed and agreed on the level of evidence for each modified statement. Each statement was assessed by the following criteria.

- ▶ *High*. Further research is very unlikely to change our confidence in the estimate of effect.
- ▶ *Moderate*. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- ▶ *Low*. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- ▶ *Very low*. Any estimate of effect is uncertain.

The conference was underwritten by an unrestricted grant from AstraZeneca Asia. In order to avoid industrial influence on the process of consensus development, only working group members were allowed in the conference room. Mandatory written disclosure of financial declared conflicts of interest within the 24 months before the meeting were obtained a priori from all voting participants and included in conference materials.

CONSENSUS STATEMENTS
A pre-endoscopy prognostic scale is useful to predict patients that require endoscopic intervention (agreement: 86.6%, level of evidence: moderate)
The ICON-UGIB states that 'Prognostic scales are recommended for early stratification of patients into low- and high-risk categories for rebleeding and mortality.'[1] Indeed, the widely studied Rockall score[2] and Blatchford score[3] use clinical, laboratory and endoscopic data to predict rebleeding and mortality. However, if scores are used only for prediction of rebleeding and mortality, they cannot be applied to the initial management of UGIB. The Blatchford and pre-endoscopic Rockall scores use only clinical and laboratory parameters to identify patients who require endoscopic intervention. In a recent study from Hong Kong, the Blatchford and pre-endoscopic Rockall scores were prospectively calculated for all patients and the need for therapeutic endoscopy was determined.[4] One thousand and eighty-seven patients were included in that study, which showed that those who need endoscopic treatment require a significantly higher Blatchford score. It is useful for predicting patients who may not need endoscopic treatment by using a threshold of 0 (low risk) and ≥1 (high risk). On the other hand, although the pre-endoscopic Rockall score was also significantly higher in those who required therapeutic endoscopy than in those who did not, it could not definitely identify those who required endoscopic treatment at a particular score. The disappointing receiver operating characteristic value for the Blatchford score in the Hong Kong study is at odds with two large UK studies.[3 5] The discrepancy is probably because these UK studies used a broader range of outcomes (transfusion, endoscopy and surgery) whereas the Hong Kong study focused on the need for endoscopic intervention, which is the most important clinical parameter in the management of UGIB. Therefore, the working group concluded that the Blatchford score should be used to assess the need for endoscopic intervention in Asian patients with UGIB. As there is only one study from Asia to examine this issue, the level of evidence was graded as moderate.

Early discharge of patients with low-risk endoscopic lesions, after consideration of comorbid factors, is generally safe and cost saving (agreement: 100%, level of evidence: moderate to low)

Can we triage patients for outpatient care or early discharge after hospitalisation based on their clinical and endoscopic findings? The Rockall score provide useful endoscopic criteria for a patient at low risk. Two studies from Asia have confirmed also that early discharge is possible without increasing the risk of morbidity and mortality.[6 7] Yet these are cohort studies and data from randomised controlled trials (RCTs) are scanty. Two small-scale prospective randomised trials from Europe suggested that early discharge of these patients from hospital did not affect the need for surgery and mortality of patients.[8 9] A recent prospective cohort study from Hong Kong also found that a Blatchford score of 0 is a good indicator of patients at low risk, who can be discharged without admission as these patients do not require endoscopic intervention.[4] However, one must differentiate between patients with ulcers at low risk *for rebleeding* against patients at low risk *for mortality*. As a survey in over 10 000 cases of peptic ulcer bleeding in Hong Kong showed three-quarters of patients died not because of uncontrolled or recurrent bleeding, but because of non-bleeding causes such as cardiopulmonary decompensation and multi-organ failure[10]; patients may have ulcers with a low risk for recurrent bleeding but die from comorbid conditions. Gastrointestinal (GI) bleeding may represents a terminal event in the multi-organ system failure. The endoscopic scoring may not apply to low-risk lesions in patients at high risk with multiple comorbidities. Patients may have a low risk for a rebleeding ulcer but age and comorbid illness determine their risk of dying. Therefore, in this statement, the working group specifies in patients with low-risk endoscopic lesions that due consideration should be given to the comorbid conditions of the patients. As there is a lack of large-scale randomised trials examining this subject, the level of evidence was graded as moderate to low. Further studies in this area are warranted.

Pre-endoscopy proton pump inhibitor is recommended where early endoscopy or endoscopic expertise is not available within 24 h (agreement: 86.7%, level of evidence: low)

A large single-centre randomised controlled study showed that pre-endoscopic use of PPIs at a high dose can downgrade the signs of haemorrhage of peptic ulcer disease.[11] As a result, fewer patients required endoscopic intervention. However, the use of PPIs under such conditions does not translate into reduction in recurrent bleeding, surgery and mortality rates. This finding was consolidated by a subsequent meta-analysis.[12] The ICON-UGIB guidelines stated that "pre-endoscopic PPI treatment may be considered to downstage the endoscopic lesion and decrease the need for endoscopic intervention but should not delay endoscopy."[1] This working group has deliberated on the implications of this statement and found that it fails to point to a specific strategy in the acute management of UGIB. Should a pre-emptive PPI be routinely given to all patients presenting with symptoms and signs of UGIB, or should it be recommended only for a selected population? The recommendation should not be constructed as discouraging clinicians who use pre-emptive PPIs for all patients with UGIB. In fact, in a decision analysis based on the Hong Kong model, the use of a high-dose PPI before endoscopy increases the upfront cost but reduces subsequent procedures and hence duration of hospital stay, and thus is still a cost-effective measure.[13] However, the working group considered that a pre-endoscopy PPI may be valuable in practices

when early endoscopy or endoscopic expertise is not available within 24 h. Under these circumstances, pre-endoscopy PPI may buy time to stabilise patients before definitive treatment can be arranged. This may be the case for some countries or communities in Asia, especially in rural areas, when medical facilities are limited or in countries where only licensed endoscopists are allowed to perform therapeutic endoscopy. In the Hong Kong study,[11] the mean time to endoscopy after the start of intravenous PPI infusion was <24 h in both PPI and placebo groups of patients. No randomised study has been carried out to compare pre-emptive PPI against early endoscopy, and thus the recommendation can only be based on logical deduction and expert opinion.

Endoscopic intervention within 24 h of onset of bleeding improves outcomes in patients at high risk (agreement: 100%, level of evidence: moderate)

Early endoscopy has been advocated for the management of UGIB but the optimal timing is still debated. Most of the data available are based on retrospective cohorts. Only three randomised trials are available, two of which came from Asia.[14–16] A systematic review concluded that endoscopy within 12 h or earlier does not result in a better clinical outcome.[17] There is no improvement in mortality, reduction in surgical need or reduced requirement for blood transfusion and very early endoscopy often leads to increased use of endoscopic treatment for advanced signs of haemorrhage, which may not be necessary.[17] Endoscopy within 24 h of presentation is recommended for management of UGIB. In most centres in developed countries, an endoscopy service is available throughout the week but not necessarily over the weekends and public holidays. Three studies from the USA recently indicated that patients with UGIB admitted over the weekends have a higher mortality, probably related to the longer endoscopy waiting time.[18–20] In Asia, when an emergency endoscopy service is available over weekends and public holidays, this 'weekend effect' is not evident.[21] Therefore, the working group recommends that all hospitals provide sufficient resources for an endoscopy service that can offer an examination within 24 h after patient presentation, including weekends and holidays. The working group discussed two exceptional circumstances in which urgent endoscopy should be considered. In patients at very high risk who are haemodynamically unstable and in patients presenting with massive haematemesis, endoscopy should be performed as soon as patients are stabilised with resuscitation. On the other hand, in patients who have critical cardiopulmonary conditions, endoscopy should be postponed until the blood pressure, heart rate and oxygenation of blood is stabilised. More randomised study to investigate the timing of endoscopy is necessary.

Endoscopic treatment plus PPI is preferable to a PPI alone in ulcers with adherent clots resistant to vigorous irrigation (agreement: 86.7%, level of evidence: moderate to low)

The optimal endoscopic treatment for a peptic ulcer with an adherent blood clot is controversial. The ICON-UGIB included two statements on this topic but the conclusion is still ambiguous. 'The finding of a clot in an ulcer bed warrants targeted irrigation in an attempt at dislodgement with appropriate treatment of the underlying lesions.'[1] On the other hand, 'the role of endoscopic treatment for ulcers with adherent clot is controversial. Endoscopic treatment may be considered, although intensive PPI treatment may be sufficient.'[1] The difficulty in this scenario is that if a clot is removable, and an underlying protuberant vessel is exposed, there is little doubt

that it should be treated with either thermal coagulation or clips.[22] However, there are occasions that the clot cannot be removed even with vigorous targeted irrigation. Not all endoscopists are comfortable to cheese-wire an adherent clot using a polypectomy snare in case it will provoke bleeding that cannot be stopped. To complicate the issue further, it is well known that sometimes it is difficult to distinguish a clot from a protuberant vessel.[23] Furthermore, the definition of adherent clot is not clearly defined. In practical terms, it is also difficult to calibrate both the vigour of irrigation and the length of time for which irrigation should be attempted before announcing failure to remove clot. In a recent post hoc analysis based on the PUB study,[24] the risk of recurrent bleeding was found to be higher in patients with peptic ulcer with an adherent clot (17.6% re-bled within 72 h OR=4.12, 95% CI 1.27 to 13.3) than in those with a protuberant blood vessel (11.3% re-bled within 72 h, OR=2.62, 95% CI 1.05 to 6.54).[25]

Based on a meta-analysis which included six studies representing 240 patients from the USA, Hong Kong, South Korea and Spain, endoscopic treatment is considered better than medical treatment for prevention of recurrent haemorrhage in patients with bleeding peptic ulcers and adherent clot.[26] The study was criticised for combining studies with a variable study design and hence the summary statistics may be misleading.[27] Recurrent bleeding is likely to be reduced and requirement for surgery decline after endoscopic intervention only in populations with a high rate of rebleeding after removing clots[27] and Asian populations belongs to this category.[24]

Based on existing evidence, the working group recommended vigorous target irrigation of a blood clot covering peptic ulcers for at least 5 min. For an adherent clot resistant to irrigation, endoscopy combined with injection treatment and thermal coagulation or mechanical device would be applied together with a PPI. There may be a chance of overtreating some patients who have a low risk of recurrent bleeding. However, existing evidence cannot differentiate between high-risk and low-risk blood vessels at the base of peptic ulcer. Further studies are needed to support this recommendation.

Second-look endoscopy is not routinely recommended after endoscopic haemostasis but should be reserved for selected patients at high risk for rebleeding (agreement: 93.3%, level of evidence: moderate to low)

The benefit of routine repeat endoscopy after endoscopic haemostasis in the management of UGIB is another contentious area. Evidence for so-called second-look endoscopy is based mostly on small-scale studies. While routine second-look endoscopy may not benefit all patients with UGIB, a selected population of patients at high risk may be benefit from this strategy.[28] Overall, the outcome measurement including recurrent bleeding, surgery, mortality, blood transfusion and length of hospital stay are not improved by the use of routine second-look endoscopy.[29] In a randomised study from Hong Kong comparing routine second-look endoscopy with repeated treatment versus routine use of high-dose PPIs, the recurrent bleeding rates at 3 days, 1 week and 1 month between the two groups were almost identical.[30] There is no difference in transfusion requirement, surgical operation or mortality using the two strategies. However, as more data become available and are pooled in a meta-analysis, with the endoscopic treatment being combined with injection treatment (which provides only temporary haemostasis) or thermal coagulation (which provides more definitive haemostasis), there is evidence suggesting that routine second-look endoscopy with thermal treatment may

make a difference.[31] Less recurrent bleeding was reported after repeated thermal coagulation (4.3%) than single endoscopy (15.7%). Unlikely thermal coagulation, second-look endoscopy with repeated injection treatment did not prevent rebleeding (17.6%) in comparison with the single treatment (20.8%). The ICON-UGIB stated that 'routine second-look endoscopy is not recommended'.[1] This panel considers that there is room for further research in this area to identify a specific group of patients for whom second-look endoscopy with definitive haemostasis with a thermal or mechanical device may be beneficial.

As an adjunct to endoscopic treatment
A. A high-dose intravenous (IV) PPI is effective in reducing rebleeding and the need for surgery (agreement: 100%, level of evidence: high).
B. A high-dose oral PPI may be effective in reducing rebleeding in Asian patients (agreement: 93.3%, level of evidence: moderate).
C. Insufficient data exist on low-dose IV PPI to justify its use (agreement: 100%, level of evidence: moderate to low).

An IV bolus followed by infusion of a high-dose PPI reduces recurrent bleeding, need for repeated endoscopy, surgery and blood transfusion. This is evident in the Cochrane meta-analysis of data, including 24 RCTs,[32 33] which showed that even mortality is reduced with the use of intravenous high-dose PPIs. Indeed, high-dose PPI infusion has already been adopted as a standard of care in many Western countries. The initial discrepancy between European and Asian studies has also been resolved by a multinational prospective randomised trial using esomeprazole in the high-dose infusion regimen in the PUB study.[24] The mortality in that study was relatively low and may not entirely reflect the real-life situation where peptic ulcer bleeding is managed in smaller centres with less experience. The use of high-dose intravenous PPIs has also been found to be cost effective in both Asia and America.[34 35]

One interesting observation in the PUB study is that a post hoc analysis suggested that the benefit of PPI is greater in those who have *H pylori* infection (rebleeding rate dropped from 8.4% to 3.7%) than in those who did not have the infection (rebleeding rate dropped from 11.8% to 9.8%).[24] This finding implies that *H pylori* infected patients may have a lower acid output and hence an augmented effect of acid suppression by PPIs. Thus it is not difficult to understand that in some Asian studies, even oral PPIs have been found to be useful in preventing recurrent bleeding from peptic ulcers.[36–40] Although the Cochrane pooled data showed that only high-dose IV PPIs, but not oral PPIs or low-dose IV PPIs, benefit patients and result in improved clinical outcome, there are obvious differences between Asian and non-Asian studies.[32 33] Two studies from Asia showed that oral PPIs as an adjunct to endoscopic treatment reduced the risk of recurrent bleeding. Javid *et al* used oral omeprazole 40 mg twice daily for 5 days and found that recurrent bleeding was reduced from 21% to 7%.[39] Kaviani *et al* also found that oral omeprazole 20 mg given every 6 h for 5 days reduced recurrent bleeding by almost 50%.[40] This observation is also considered in the ICON-UGIB, which suggest that oral doses of PPIs equivalent to four times the standard daily oral dose can be considered.[1]

Although strong evidence demonstrates the efficacy of high-dose IV PPI treatment after successful endoscopy, it is not possible to draw definite conclusions about the efficacy of a lower IV dose of PPI. Meta-analysis by Laine and McQuaid found that lower doses of PPIs may reduce rebleeding compared

with placebo or no treatment.[41] A recent meta-analysis comparing high-dose and non-high-dose PPIs after endoscopic treatment in patients with bleeding peptic ulcers[42] concluded that there was no difference in the outcome. The study, however, was limited by multiple methodological flaws, such as including inappropriate studies and insufficient sample size.[43] In Korea, studies comparing low-dose IV PPIs with a standard high-dose regimen have been carried out but the results are conflicting.[44] Head-to-head comparisons and subgroup analysis of high versus lower IV doses are also underpowered. Therefore, a low-dose regimen of IV bolus or infusion of PPIs cannot be recommended.

Angiographic embolisation should be considered as an alternative to surgery in patients for whom endoscopic haemostatic treatment has failed (agreement: 100%, level of evidence: low)

When a first endoscopy fails to control peptic ulcer bleeding, surgery offers a better chance to secure haemostasis but repeated endoscopic treatment carries fewer complications.[45] However, because of advanced age and serious comorbid illnesses, not all patients are suitable candidates for surgery. Angiographic embolisation has been used in the treatment of peptic ulcer bleeding. In a French series of 60 patients, embolisation treatment controlled gastroduodenal bleeding in 95% of cases after endoscopic failure.[46] There is no solid evidence to support the use of angiographic embolisation as an alternative to surgery after endoscopic treatment has failed to control bleeding of UGIB. A retrospective study from Italy showed no significant differences between embolisation treatment and surgery for rates of rebleeding, surgery or mortality.[47] Another retrospective study from Hong Kong also showed that angiographic embolisation is valuable for uncontrolled ulcer bleeding.[48] Gelatin sponges, polyvinyl alcohol, cyanoacrylate have been used for embolisation but coils are most commonly used. It is well known that because of the vascular nature of the stomach and duodenum, more than one vessel will often need to be embolised to control bleeding. Recurrence of bleeding after a successful procedure is not uncommon. The working group recommends that clinicians should consider angiographic embolisation as a possible alternative treatment, especially for patients with high surgical risk. Since there is a lack of solid evidence, the working group suggests that angiographic embolisation should be considered as an alternative only if expertise is available. A prospective randomised study is urgently needed to shed light on the efficacy of this treatment.

Among patients with arthritis and a history of ulcer bleeding who require NSAIDs

A. Both non-selective NSAID plus a PPI and a COX-2 selective NSAID reduce rebleeding but substantial risk remains (agreement: 100%, level of evidence: high).
B. A COX-2 selective NSAID plus a PPI offers the best available upper GI protection (agreement: 100%, level of evidence: moderate).

It is known that in patients who have a history of peptic ulcer bleeding, the use of both a COX-2 selective NSAID and an NSAID plus a PPI have reduced but not eliminated risk of recurrent bleeding. In a study which randomised patients to receive either diclofenac 75 mg twice daily plus omeprazole 20 mg per day or celecoxib 200 mg twice daily,[49] over a period of 6 months, rebleeding occurred in 6.4% and 4.9%, and recurrent ulcer reported in 26% and 19%, respectively. These are still substantial proportions of patients and therefore, it is necessary

to find a treatment strategy to further reduce risk of recurrent bleeding from peptic ulcers with the use of analgesics. In a randomised controlled study from Asia, in which H pylori negative patients with a history of peptic ulcer bleeding were assigned to receive either celecoxib 200 mg twice daily plus esomeprazole twice daily or celecoxib 200 mg twice daily plus placebo, recurrent rebleeding was reported in almost 9% in the placebo group but 0% in the PPI group.[50] A similar study using celecoxib 200 mg daily in comparison with naproxen 750 mg daily plus lansoprazole 30 mg daily produced an almost identical result—that is, the rates of ulcer complications were similar but still substantial.[51] However, a head-to-head comparison of a COX-2 selective NSAID plus PPI and an NSAID plus PPI is lacking. Despite this limitation, a COX-2 selective NSAID plus PPI probably offers the best available option because this strategy has been shown to be better than a COX-2 selective NSAID alone[50] and there is evidence that NSAIDs plus PPIs provide upper GI protection equivalent to that of a COX-2 inhibitor alone.[49]

Among aspirin users with high cardiothrombotic risk who develop ulcer bleeding, aspirin should be resumed as soon as possible once haemostasis is established (agreement: 86.6%, level of evidence: moderate)

Discontinuing antiplatelet treatment in patients with high cardiothrombotic risk increases the likelihood of occurrence of an adverse cardiovascular event. This phenomenon has been well demonstrated in a small retrospective study[52] and more recently a prospective RCT.[53] This Asian study added a high-dose intravenous PPI followed by an oral PPI to low-dose aspirin, and showed that patients whose aspirin treatment was discontinued after endoscopic haemostasis of ulcer bleeding had a lower risk of recurrent bleeding but significantly higher mortality. Most of the mortality was related to cardiovascular and cerebrovascular death. In this study, however, the prolonged discontinuation of aspirin for 8 weeks was a concern. There was no evidence to suggest that discontinuation for 30 days or shorter will increase mortality. Currently, there is a lack of clinical data to provide guidance on a 'safe' period of discontinuation of aspirin or antiplatelet agents. Given the evidence of potential harm associated with discontinuation of antiplatelet agents, the working group recommends that aspirin should be resumed as soon as possible after achieving endoscopic haemostasis within a few days after endoscopy. As the first 3 days after index bleeding account for about 80% of rebleeding occurrence,[53] and as the antiplatelet activity of aspirin is irreversible until new platelets are being produced in the bone marrow, it is sensible to restart aspirin at day 3—5 provided that the patient's haemodynamic condition is stable.

Data are lacking in the literature to indicate whether patients receiving clopidogrel should also resume the drug early after bleeding is brought under control. In view of the similar antiplatelet activity of clopidogrel and aspirin, it might be prudent to stop clopidogrel also for 3—5 days and resume after stabilisation. There is also no evidence to guide the treatment of patients taking dual antiplatelet agents (eg, aspirin plus clopidogrel) who develop upper GI bleeding. Patients receiving clopidogrel usually have a previous coronary stent placement. The optimal timing of resuming clopidogrel or dual antiplatelet treatment needs to be individualised because it depends on the duration of stent placement (eg, a coronary stent placed within 30 days carries a much higher risk of thrombosis than a stent placed beyond 30 days), the type of stent (ie, drug-eluting vs bare metal stents) and, probably, the ease of endoscopic

haemostasis. It is therefore not possible to draw up any consensus statement on the discontinuation of clopidogrel or dual antiplatelet agents in the acute phase of upper GI bleeding. Further studies are urgently needed in this area.

Clopidogrel alone is not a safer alternative than the combination of low-dose aspirin plus PPI in patients with increased risk of ulcer bleeding (agreement: 100%, level of evidence: moderate)

With the ageing population world wide, many patients with cardiovascular or cerebrovascular diseases require long-term antiplatelet agents to prevent vascular thrombosis. The CAPRIE study, with a large study population and careful study design, has convincingly shown that clopidogrel is a safer drug to use than aspirin in patients with vascular disorder, leading to less GI bleeding.[54] However, it is worth pointing out that the CAPRIE study targeted a population at average risk rather than patients at high risk for UGIB. Conversely, it has been shown that patients receiving clopidogrel had an increased incidence of recurrent upper GI bleeding than patients receiving low-dose aspirin combined with a PPI. In an Asian randomised controlled study recruiting patients with a history of peptic ulcer bleeding who required antiplatelet agents, clopidogrel increased the risk of recurrent bleeding more than 10 times.[55] However, the incidence of lower GI bleeding was the same with or without a PPI. Therefore, a PPI protects the upper GI tract from further injury by aspirin and the combination is safer than clopidogrel monotherapy. In this study, aspirin 80 mg daily was used. A similar study also from Hong Kong using esomeprazole 20 mg and aspirin 100 mg per day versus clopidogrel 75 mg daily in patients with history of peptic ulcer bleeding and treated *H pylori* infection showed a similar result.[56] The risk of upper GI bleeding with low-dose aspirin is dose related.[57] It is uncertain whether PPIs can confer the same degree of protection as higher doses of aspirin. Irrespective of the practice in Asian or Western countries, it is generally agreed that there is no added cardiovascular benefit of using aspirin beyond 160 mg daily. The interaction of clopidogrel and a PPI may hamper the antiplatelet activity of the former and hence is not favoured. The working group also discussed the cost of aspirin plus a PPI in comparison with clopidogrel; the former prescription is cheaper in most Asian countries.

Among patients receiving clopidogrel and aspirin as dual treatment, prophylactic use of a PPI reduces the risk of adverse GI events (agreement: 81.25%, level of evidence: moderate)

Use of dual antiplatelet agents is increasing as patients with acute coronary syndrome treated by coronary stenting are prescribed a combination of aspirin and clopidogrel for up to 12 months based on the PCI-CURE study.[58] In the same study, however, it is obvious that the two antiplatelet agents together increase the risk of major GI bleeding from 0.7% to 1.3%. Yet, clopidogrel, a prodrug that needs to be metabolised in the liver by cytochrome P450 system (particularly 2C19), competes with PPIs, which are also metabolised by CYP2C19, and this has raised major concern. Loss of antiplatelet effect due to this biological interaction has been demonstrated in ex vivo studies on the platelet reactivity index.[59–61] Retrospective case—control and cohort studies also indicated that PPI use leads to increased thrombosis of coronary stents and is associated with increase recurrent myocardial infarction.[62–65] On the other hand, other studies reported no such association.[66 67]

One of the explanations of this conflicting result is that the studies are mostly retrospective cohort studies in which risk factors for cardiovascular diseases such as smoking, hypertension, cholesterol levels, etc, were not controlled. Patients who were prescribed a PPI in addition to a dual antiplatelet agent may merely reflect the fact that those patients had more serious comorbid illness and therefore a PPI is merely a surrogate for more serious morbid illness. In a meta-analysis of 23 studies involving over 93 000 patients, analysis of propensity-matched or randomised trials showed no association between cardiovascular risk and PPI use. In contrast, other observational studies showed a significant association. It is worthwhile pointing out that the meta-analysis did not show significant association between PPI use and overall mortality.[68] As indicated by an editorial recently, however, the existing regulatory decisions are not based on quality clinical studies and have relied more on surrogate markers such as in vitro platelet-inhibition studies.[69] The only way to settle this issue is to conduct a carefully designed randomised study comparing dual antiplatelet agents (including clopidogrel) with or without a PPI for cardiovascular and GI adverse events. This was indeed done in the COGENT trial which was designed specifically to examine this topic.[70] This multicentre randomised double-blind, double-dummy, placebo-controlled study showed that PPIs reduced GI bleeding but did not increase cardiovascular risk. Unfortunately, the study was terminated prematurely for financial reasons. Although this was an unfinished trial with incomplete enrolment and truncated followed up of up to 133 days (median follow-up), the result gave the best available evidence that the interaction between a PPI and clopidogrel has, at most, a modest effect on thrombosis. Based on these results, the working group recommends adding a PPI to dual antiplatelet agents when indicated.

FUTURE RESEARCH

The management of upper GI bleeding has come a long way from the advent of endoscopic treatment, use of potent acid-suppressing agents and the complications of NSAID and antiplatelet usage. There is a pressing need for future studies to elucidate the effect of oral high-dose PPIs in prevention of recurrent bleeding, the optimal period of discontinuation of aspirin, the best protection for those who require double antiplatelet agents. On the endoscopic front, a simple scoring system to identify high-risk patients for endoscopic intervention, the role of angiographic embolisation when endoscopy fails to control bleeding, the selection criteria for high-risk patients who may require second-look endoscopy will be important future topics for research.

DISSEMINATION STRATEGIES

This consensus statement which is tailored for the Asian population will be disseminated by the following means: 1. presentations at future APDW meetings as forums to an audience of predominantly Asian clinicians and 2. copies of this statement will be sent to national societies/associations of gastroenterology and endoscopists for their iteration and dissemination. It is hope that the consensus strategies will be updated regularly and adopted by health authorities in the Asia-Pacific region to improve the care of patients with UGIB.

REFERENCES

1. **Barkun A,** Bardou M, Kuipers EJ, *et al*. International consensus recommendations on the management of patients with non-variceal upper gastrointestinal bleeding (ICON-UGIB). *Ann Intern Med* 2010;**152**:101—13.

2. **Rockall TA,** Logan RF, Devlin HB, *et al*. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996;**38**:316—21.
3. **Blatchford O,** Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet* 2000;**356**:1318—21.
4. **Pang SH,** Ching JY, Lau JY, *et al*. Comparing the Blatchford and pre-endoscopic Rockall score in predicting the need for endoscopic therapy in patients with upper GI hemorrhage. *Gastrointest Endosc* 2010;**71**:1134—40.
5. **Stanley AJ,** Ashley D, Dalton HR, *et al*. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. *Lancet* 2009;**373**:42—7.
6. **Lai KC,** Hui WM, Wong BC, *et al*. A retrospective and prospective study on the safety of discharging selected patients with duodenal ulcer bleeding on the same day as endoscopy. *Gastrointest Endosc* 1997;**45**:26—30.
7. **Hsu PI,** Lai KH, Lin XZ, *et al*. When to discharge patients with bleeding peptic ulcers: a prospective study of residual risk of rebleeding. *Gastrointest Endosc* 1996;**44**:382—7.
8. **Cipoletta L,** Bianco MA, Rotondano G, *et al*. Outpatient management for low-risk non-variceal upper GI bleeding: a randomized controlled trial. *Gastrointest Endosc* 2002;**55**:1—5.
9. **Brullet E,** Campo R, Calvet X, *et al*. A randomized study of the safety of outpatient care patients with bleeding peptic ulcer treated by endoscopic injection. *Gastrointest Endosc* 2004;**60**:15—21.
10. **Sung JJ,** Tsoi KK, Ma TK, *et al*. Causes of mortality in patients with peptic ulcer bleeding: a prospective cohort study of 10,428 cases. *Am J Gastroenterol* 2010;**105**:84—9.
11. **Lau JY,** Leung WK, Wu JC, *et al*. Omeprazole before endoscopy in patients with gastrointestinal bleeding. *N Engl J Med* 2007;**356**:1631—40.
12. **Sreedharan A,** Martin J, Leontiadis G, *et al*. Does proton pump inhibitor (PPI) treatment initiated before endoscopy work in unselected upper gastrointestinal bleeding? A Cochrane systematic review update. *Cochrane Database Syst Rev* 2010; (7):CD005415.
13. **Tsoi KK,** Lau JY, Sung JJ. Cost-effectiveness analysis of high-dose omeprazole infusion before endoscopy for patients with upper-GI bleeding. *Gastrointest Endosc* 2008;**67**:1056—63.
14. **Lin H,** Wang K, Perng CL, *et al*. Early or delayed endoscopy for patients with peptic ulcer bleeding: a prospective randomized study. *J Clin Gastroenterol* 1996;**22**:267—71.
15. **Lee JG,** Turnipseed S, Romano PS, *et al*. Endoscopy-based triage significantly reduces hospitalization rate and costs of treating upper GI bleeding: a randomized controlled trial. *Gastrointest Endosc* 1999;**50**:755—61.
16. **Bjorkman DJ,** Zaman A, Fennerty MB, *et al*. Urgent vs elective endoscopy for acute non-variceal upper GI bleeding: an effectiveness study. *Gastrointest Endosc* 2004;**60**:1—8.
17. **Tsoi KK,** Ma TK, Sung JJ. Endoscopy for upper gastrointestinal bleeding: how urgent is it? *Nat Rev Gastroenterol Hepatol* 2009;**6**:463—9.
18. **Shaheen AA,** Kaplan GG, Myers RP. Weekend versus weekday admission and mortality from gastrointestinal hemorrhage caused by peptic ulcer disease. *Clin Gastroenterol Hepatol* 2009;**7**:303—10.
19. **Dorn SD,** Shah ND, Berg BP, *et al*. Effect of weekend admission on gastrointestinal outcomes. *Dig Dis Sci* 2010;**55**:1658—66.
20. **Ananthakrishnan AN,** McGinley EL, Saeian K. Outcomes of weekend admissions for upper gastrointestinal hemorrhage: a nationwide analysis. *Clin Gastroenterol Hepatol* 2009;**7**:296—302.
21. **Tsoi KK,** Pang SH, Chiu PW, *et al*. The risk of ulcer-related death in relation to hospital admission on public holidays: a cohort study on 10,428 cases of upper gastrointestinal bleeding in Hong Kong. *Gastrointest Endosc* 2010;**71**:AB141.
22. **Sung JJ,** Chan FK, Lau JY, *et al*. The effect of endoscopic therapy in patients receiving omeprazole for bleeding ulcers with nonbleeding visible vessels or adherent clots: a randomized comparison. *Ann Intern Med* 2003;**139**:237—43.
23. **Lau JY,** Chung SC, Leung JW, *et al*. The evolution of stigmata of hemorrhage in bleeding peptic ulcers: a sequential endoscopic study. *Endoscopy* 1998;**30**:513—18.
24. **Sung JJ,** Barkun A, Kuipers EJ, *et al*; Peptic Ulcer Bleed Study Group. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2009;**150**:455—64.
25. **Jensen DM,** Ahlbom H, Eklund S, *et al*. Rebleeding risk for oozing peptic ulcer bleeding (PUB) in a large international study—a reassessment based upon a multivariate analysis. *Gastrointest Endosc* 2010;**71**:AB117.
26. **Kahi CJ,** Jensen DM, Sung JJ, *et al*. Endoscopic therapy versus medical therapy for bleeding peptic ulcer with adherent clot: a meta-analysis. *Gastroenterology* 2005;**129**:855—62.
27. **Laine L.** Systematic review of endoscopic therapy for ulcers with clots: can a meta-analysis be misleading. *Gastroenterology* 2005;**129**:2127.
28. **Saeed ZA,** Cole RA, Ramirez FC, *et al*. Endoscopic retreatment after successful initial hemostasis prevents ulcer rebleeding: a prospective randomized trial. *Endoscopy* 1996;**28**:288—94.
29. **Tsoi KK,** Chiu PW, Sung JJ. Endoscopy for upper gastrointestinal bleeding: is routine second look necessary? *Nat Rev Gastroenterol Hepatol* 2009;**6**:717—22.
30. **Chiu P,** Choi C, Kwong K-H, *et al*. The effect of scheduled second endoscopy against intravenous high dose omeprazole infusion as an adjunct to therapeutic endoscopy in prevention of peptic ulcer rebleeding—a prospective randomized study. *Gastroenterology* 2006;**130**:A121.
31. **Tsoi KK,** Chan HC, Chiu PW, *et al*. Second-look endoscopy with thermal coagulation or injections for peptic ulcer bleeding: a meta-analysis. *J Gastroenterol Hepatol* 2010;**25**:8—13.
32. **Leontiadis GI,** Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syst Rev* 2006;(1):CD002094.
33. **Leontiadis G,** Martin J, Sharma V, *et al*. Proton pump inhibitor (PPI) treatment for peptic ulcer (PU) bleeding: an updated Cochrane metaanalysis of randomized controlled trials (RCTs). *Gastroenterology* 2009;**136**:A134.
34. **Barkun AN,** Herba K, Adam V, *et al*. High-dose intravenous proton pump inhibition following endoscopic therapy in the acute management of patients with bleeding peptic ulcers in the USA and Canada: a cost-effectiveness analysis. *Aliment Pharmacol Ther* 2004;**19**:591—600.
35. **Lee KK,** You JH, Wong IC, *et al*. Cost-effectiveness analysis of high-dose omeprazole infusion as adjuvant therapy to endoscopic treatment of bleeding peptic ulcer. *Gastrointest Endosc* 2003;**57**:160—4.
36. **Khuroo MS,** Yattoo GN, Javid G, *et al*. A comparison of omeprazole and placebo for bleeding peptic ulcer. *N Engl J Med* 1997;**336**:1054—8.
37. **Jang J,** Dong S, Jung J, *et al*. High-dose oral proton pump inhibitor is as effective as intravenous administration in the aspect of increasing pH and reducing rebleeding after endoscopic treatment of bleeding peptic ulcers. *Gastroenterology* 2006;**103**:A467.
38. **Bajaj JS,** Dua KS, Hanson K, *et al*. Prospective, randomized trial comparing effect of oral versus intravenous pantoprazole on rebleeding after nonvariceal upper gastrointestinal bleeding: a pilot study. *Dig Dis Sci* 2007;**52**:2190—4.
39. **Javid G,** Masoodi I, Zargar SA, *et al*. Omeprazole as adjuvant therapy to endoscopic combination therapy for treating bleeding peptic ulcer. *Am J Med* 2001;**111**:280—4.
40. **Kaviani MJ,** Hashemi MR, Kazemifar AR, *et al*. Effect of oral omeprazole in reducing re-bleeding in bleeding peptic ulcers: a prospective, double-blind, randomized, clinical trial. *Aliment Pharmacol Ther* 2003;**17**:211—16.
41. **Laine L,** McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analysis of randomized controlled trial. *Clin Gastroenterol Hepatol* 2009;**7**:33—47.
42. **Wang CH,** Ma MHM, Chou HC, *et al*. High-dose vs non-high-dose proton pump inhibitors after endoscopic treatment in patients with bleeding peptic ulcer: a systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2010;**170**:751—8.
43. **Calvet X,** Barkun A, Bardou M, *et al*. High-dose vs non-high-dose PPIs after endoscopic treatment in patients with bleeding peptic ulcer: current evidence is insufficient to claim equivalence. *Arch Intern Med* 2010;**170**:1698—9 author reply 1700.
44. **Choi KD,** Kim N, Jang IJ, *et al*. Optimal dose of intravenous pantoprazole in patients with peptic ulcer bleeding requiring endoscopic hemostasis in Korea. *J Gastroenterol Hepatol* 2009;**24**:1617—24.
45. **Lau JY,** Sung JJ, Lam YH, *et al*. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. *N Engl J Med* 1999;**340**:751—6.
46. **Loffroy R,** Guiu B, D'Athis P, *et al*. Arterial embolotherapy for endoscopically unmanageable acute gastroduodenal hemorrhage: predictors of early rebleeding. *Clin Gastroenterol Hepatol* 2009;**7**:515—23.
47. **Ripoll C,** Banares R, Beceiro I, *et al*. Comparison of transcatheter arterial embolization and surgery for treatment of bleeding peptic ulcer after endoscopic treatment failure. *J Vasc Interv Radiol* 2004;**15**:447—50.
48. **Wong TC,** Chiu PW, Wong KT, *et al*. A comparison of transcatheter arterial embolisation to surgery after failed endoscopic hemostasis to bleeding peptic ulcers. *Gastrointest Endosc* 2010;**71**:AB113—14.
49. **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.
50. **Chan FK,** Wong VW, Suen BY, *et al*. Combination of a cyclo-oxygenase-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.
51. **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.
52. **Spertus JA,** Kettelkamp R, Vance C, *et al*. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation* 2006;**113**:2803—9.
53. **Sung JJ,** Lau JY, Ching JY, *et al*. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2010;**152**:1—9.
54. **CAPRIE Steering Committee.** A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events. *Lancet* 1996;**348**:1329—39.
55. **Chan FK,** Ching JY, Hung LC, *et al*. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005;**352**:238—44.
56. **Lai KC,** Chu KM, Hui WM, *et al*. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. *Clin Gastroenterol Hepatol* 2006;**4**:860—5.
57. **Weil J,** Colin-Jones D, Langman M, *et al*. Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ* 1995;**310**:827—30.
58. **Mehta SR,** Yusuf S, Peters RJ, *et al*. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;**358**:527—33.
59. **Yun KH,** Rhee SJ, Park HY, *et al*. Effect of omeprazole on the antiplatelet activity of clopidogrel. *Int Heart J* 2010;**51**:13—16.

60. **Sibbing D,** Morath T, Stegherr J, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. Thromb Haemost 2009;**101**:714—19.
61. **Neubauer H,** Engelhardt A, Kruger JC, et al. Pantoprazole does not influence the antiplatelet activity of clopidogrel—a whole blood aggregometry study after coronary stenting. J Cardiovasc Pharmacol 2010;**56**:91—7.
62. **Gaglia MA Jr,** Torguson R, Hanna N, et al. Relation of proton pump inhibitor use after percutaneous conronary intervention with drug-eluting stents to outcomes. Am J Cardiol 2010;**105**:833—8.
63. **Juurlink DN,** Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;**180**:713—18.
64. **Ho PM,** Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009;**301**:937—44.
65. **Huang CC,** Chen YC, Leu HB, et al. Risk of adverse outcomes in Taiwan associated with concomitant use of clopidogrel and proton pump inhibitors in patients who received percutaneous coronary intervention. Am J Cardiol 2010;**105**:1705—9.
66. **O'Donoghue ML,** Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. Lancet 2009;**374**:989—97.
67. **Ray WA,** Murray KT, Griffin MR, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. Ann Intern Med 2010;**152**:337—45.
68. **Kwok CS,** Loke YK. Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. Aliment Pharmacol Ther 2010;**31**:810—23.
69. **de Aquino Lima JP,** Brophy JM. Conflicting evidence: what's a clinician to do? Ann Intern Med 2010;**153**:413—15.
70. **Bhatt DL,** Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010;**363**:1909—17.

Editor's quiz: GI snapshot

To resect or not to resect? That is the question

CLINICAL PRESENTATION

A 54-year-old Caucasian female, with a strong family history of renal cell carcinoma, presented with a left kidney lesion. She had a hysterectomy 20 years ago and no significant history of oral contraceptive use. During the current evaluation, she was found to have two hypervascular lesions in the left lobe of the liver in addition to a fatty liver on CT scan as well as MRI (figure 1A—C). The largest lesion was 2 cm in size. She was asymptomatic. Physical examination showed an obese woman with body mass index of 35.6 with an otherwise normal exam. Her laboratory results showed an aspartate aminotransferase of 88 U/l, alanine aminotransferase of 75 U/l, alkaline phosphatase of 93 U/l, total
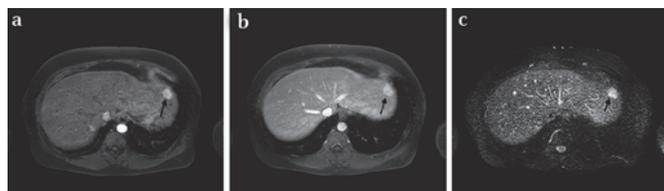

Figure 3 Haemangoima-like area from the mass. The lesion also showed prominant steatosis.

bilirubin of 0.6 mg/dl and direct bilirubin of 0.2 mg/dl. Her albumin, leucocytes, haemoglobin and platelets were all normal. She underwent a left nephrectomy. She also underwent a hepatectomy of segments 2 and 3 due to suspicion of metastatic disease. The pathology from the liver lesions is shown in figures 2 and 3.

QUESTION

What is the diagnosis of the liver lesions?
See page 1235 for answer

Figure 1 (A) MRI of the liver showing hyperintensity of one of the lesions (arrow) on T1-weighted gradient echo fat suppressed MR, arterial phase. (B) MRI of the liver showing hyperintensity of one of the lesions (arrow) on T1-weighted gradient echo fat suppressed MR, venous phase. Note the mild washout of the contrast in the lesion compared to the arterial phase image. (C) MRI of the liver on T2-weighted fast spin echo fat suppressed MR, showing strong hyperintensity of the lesion, with absence of central scar.
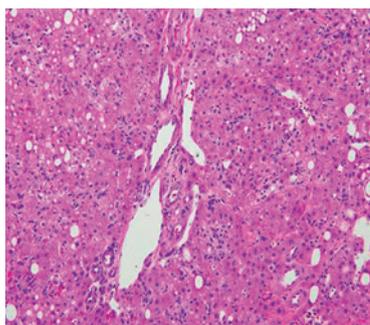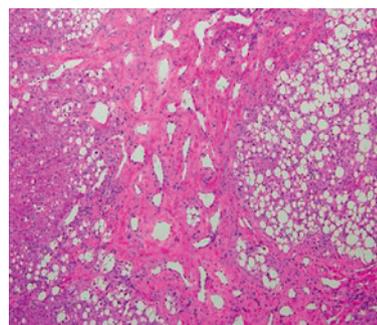
Mazen Noureddin,[1] **David E Kleiner,**[2] **Ahmed M Gharib,**[3] **Gennady Bratslavsky,**[4] **Theo Heller**[1]

[1]Liver Diseases Branch, The National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Maryland, USA; [2]Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Maryland, USA; [3]Integrative Cardiovascular Imaging Section, The National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Maryland, USA; [4]Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Maryland, USA

Correspondence to Dr Mazen Noureddin, Liver Diseases Branch, The National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 10 Center Drive, Bldg 10 Room 4-5722, Clinical Center, Bethesda, Maryland 20892, USA; noureddinm@niddk.nih.gov

Figure 2 Section of one of the hepatic masses showing a portal-like area with arteries and veins but no bile ducts.