

Leading article

Statements of the Malaysian Society of Gastroenterology & Hepatology and the National Heart Association of Malaysia task force 2012 working party on the use of antiplatelet therapy and proton pump inhibitors in the prevention of gastrointestinal bleeding

Huck-Joo TAN,* Sanjiv MAHADEVA,[†] Jayaram MENON,[‡] Wai Kiat NG,[§] Imran ZAINAL ABIDIN,[†] Francis KL CHAN[¶] & Khean-Lee GOH[†]

*Sunway Medical Centre, Selangor, [†]University of Malaya, [§]Pantai Medical Centre, Kuala Lumpur, [‡]Queen Elizabeth Hospital, Sabah, Malaysia; and [¶]Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong SAR, China

The working party statements aim to provide evidence and guidelines to practising doctors on the use of antiplatelet therapy and proton pump inhibitors (PPIs) in patients with cardiovascular risk as well as those at risk of gastrointestinal (GI) bleeding. Balancing the GI and cardiovascular risk and benefits of antiplatelet therapy and PPIs may sometimes pose a significant challenge to doctors. Concomitant use of anti-secretory medications has been shown to reduce the risk of GI bleeding but concerns have been raised

on the potential interaction of PPIs and clopidogrel. Many new data have emerged on this topic but some can be confusing and at times controversial. These statements examined the supporting evidence in four main areas: rationale for antiplatelet therapy, risk factors of GI bleeding, PPI–clopidogrel interactions and timing for recommencing antiplatelet therapy after GI bleeding, and made appropriate recommendations.

KEY WORDS: antiplatelet therapy, gastrointestinal bleeding, proton pump inhibitor.

INTRODUCTION

This working party statement was developed by the Malaysian Society of Gastroenterology and Hepatology (MSGH) and the National Heart Association of

Malaysia (NHAM) to provide evidence and guidelines to practising doctors on the use of antiplatelet therapy and proton pump inhibitors (PPIs) in patients with cardiovascular (CV) risk as well as those at risk of gastrointestinal (GI) bleeding. Many new data have emerged on this topic but some can be confusing and at times controversial. The statements of the working party aimed to address some of these issues and clarify them as much as possible. It is our hope that they will benefit not only doctors practising in Malaysia but also those in other parts of the world.

Antiplatelet drugs are widely used in the prevention and management of atherosclerotic CV disease.

Correspondence to: Huck-Joo TAN, Sunway Medical Centre, 5 Jalan Lagoon Selatan, Bandar Sunway, Petaling Jaya, Selangor 46150, Malaysia. Email: hucktjan@hotmail.com

© 2012 The Authors
Journal of Digestive Diseases © 2012 Chinese Medical Association
Shanghai Branch, Chinese Society of Gastroenterology, Renji
Hospital Affiliated to Shanghai Jiaotong University School of
Medicine and Wiley Publishing Asia Pty Ltd.

Table 1. Summary of findings and recommendations on antiplatelet therapy and gastrointestinal (GI) bleeding

A. Rationale for antiplatelet therapy
1. Clopidogrel and aspirin dual therapy is superior to aspirin alone in reducing CV events in ACS and PCI but significantly increases the risk of GI bleeding.
2. Dual antiplatelet therapy with prasugrel or ticagrelor (and aspirin) is more effective than clopidogrel and aspirin in preventing major CV events in ACS with PCI, but it increases the risk of major bleeding.
B. Antiplatelet and GI bleeding
1. Antiplatelet drugs increase the risk of GI bleeding.
2. PPIs are superior to H ₂ RA in the primary and secondary prevention of aspirin-induced ulcer.
3. <i>H. pylori</i> detection and eradication is recommended for high GI bleeding risk patients before commencing long-term aspirin.
4. Continuing PPIs after <i>H. pylori</i> eradication is superior to <i>H. pylori</i> eradication alone in preventing recurrent ulcer bleeding in patients on aspirin.
5. In patients with previous upper GI bleeding, PPIs should be added to antiplatelet therapy to prevent recurrent ulcer bleeding.
6. Patients with high risk for GI bleeding requiring antiplatelet therapy should be on long-term PPIs.
C. PPI–clopidogrel interaction
1. PPIs inhibit activation of clopidogrel via CYP2C19 pathway based on <i>in vitro</i> studies.
2. There is no consistent evidence that any single particular PPI interacts adversely with clopidogrel.
D. Recommencing antiplatelet therapy following bleeding
1. Aspirin should be recommenced early to reduce CV mortality although the risk of GI bleeding increases

CV, cardiovascular; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; PPIs, proton pump inhibitors; H₂RA, H₂-receptor antagonist; *H. pylori*, *Helicobacter pylori*; CYP2C19, cytochrome P450 2C19.

Aspirin is the most commonly used antiplatelet agent because of its wide availability, low cost and good efficacy. It works by inhibiting the enzyme cyclooxygenase (COX) and reducing the production of thromboxane A₂, a stimulator of platelet aggregation.¹ It is used in the acute setting of myocardial infarction (MI) as well as in the primary and secondary prevention of CV diseases.² The other class of antiplatelet agent used is the adenosine diphosphate (ADP) receptor inhibitors. They can be further divided into thienopyridines such as ticlopidine, clopidogrel, prasugrel and elinogrel, and non-thienopyridines such as ticagrelor and cangrelor. These classes of drug are P2Y₁₂ antagonists binding to the P2Y₁₂ receptors located on the surface of the platelet cell, which in turn lead to the binding of ADP, thus inhibiting platelet aggregation.¹ Ticlopidine was the first thienopyridine introduced to clinical practice. It has proven to be an effective antiplatelet drug but its potential severe side effects such as neutropenia and thrombotic thrombocytopenic purpura had limited its use and has largely been replaced by clopidogrel. Thienopyridines are less likely to cause GI hemorrhage and GI upset.³ A landmark trial (CAPRIE)⁴ has demonstrated that clopidogrel alone is superior to aspirin using a composite end point of ischemic stroke, MI and peripheral arterial disease. On subgroup analysis, however, no therapeutic advantage has been found of clopidogrel

monotherapy over aspirin in preventing ischemic stroke or MI.

Balancing the GI and CV risk and benefits of antiplatelet therapy and PPIs may pose a significant challenge to doctors. The concomitant use of anti-secretory medications has been shown to reduce the risk of GI bleeding but concerns have been raised on the potential interaction of PPIs and clopidogrel. The following statements by MSGH and NHAM are based on the current available evidence to address the different aspects of antiplatelet therapy and GI bleeding: the rationale for antiplatelet therapy, the risk of GI bleeding associated with antiplatelet therapy, PPI–clopidogrel interaction and the timing for recommencing antiplatelet therapy following GI bleeding (Table 1).

RATIONALE OF ANTIPLATELET THERAPY

1. Clopidogrel and aspirin dual therapy is superior to aspirin alone in reducing CV events in acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI) but significantly increases the risk of GI bleeding

In patients presenting with non-ST elevation ACS the Clopidogrel in Unstable angina to prevent Recurrent

Events (CURE) trial⁵ demonstrated an 18% lower incidence of death, MI or stroke in patients given dual antiplatelet therapy (clopidogrel plus aspirin) than in those treated with aspirin alone. Not unexpectedly, there were more patients with major bleeding in the dual therapy group (3.7%) than in the aspirin monotherapy group (2.7%) (relative risk [RR] 1.38, 95% confidence interval [CI] 1.13–1.67; $P=0.001$). A Cochrane Database Systematic Review^{6,7} also showed a clear benefit of dual therapy in patients with acute non-segment (ST) elevation coronary syndrome but the evidence was not good for high CV-risk patients, that is, those with multiple risk factors for ischemic heart disease but who did not present acutely with coronary syndrome.

In patients presenting with acute ST elevation MI, both the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)⁸ and the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction Trial (CLARITY-TIMI)⁹ showed clearly the benefit of dual antiplatelet therapy *vs* aspirin monotherapy, with an 8% and 31% lower incidence of death, MI and stroke, respectively. Dual antiplatelet therapy is recommended for at least one year followed by aspirin indefinitely.

For patients with stable coronary artery disease, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) Trial¹⁰ demonstrated that dual antiplatelet therapy with clopidogrel and aspirin is not significantly better than aspirin alone in preventing death, MI or stroke in more than 15 000 patients (secondary prevention). However, it is unknown whether dual antiplatelet therapy is superior to aspirin monotherapy as primary prevention in high-risk patients with multiple risk factors for ischemic heart disease but with no prior history of it.

Two important trials provided evidence for the benefit of clopidogrel and aspirin in patients undergoing PCI. A sub-study of CURE, PCI-CURE,¹¹ examined the effects of clopidogrel and aspirin dual therapy in 2658 patients with non-ST elevation ACS undergoing PCI. There was a 31% RR reduction in the incidence of CV death, MI or the need for re-vascularization in patients pretreated with clopidogrel for a mean period of 10 days. Similarly the Clopidogrel for the Reduction of Events During Observation (CREDO) Trial¹² showed clearly the benefit of clopidogrel and aspirin with a 3% absolute reduction in death, MI or stroke compared with aspirin alone.

2. Dual antiplatelet therapy with prasugrel or ticagrelor (and aspirin) is more effective than clopidogrel and aspirin in preventing major CV events in ACS with PCI, but it increases the risk of major bleeding

The Trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel – thrombolysis in MI (TRITON-TIMI 38) trial studied 13 608 patients with moderate to high risk of ACS and compared the efficacy of prasugrel with aspirin *vs* clopidogrel and aspirin in patients undergoing PCI with various stents. Prasugrel plus aspirin was found to be superior in reducing the primary end point of CV death and non-fatal MI in patients with ACS (9.9% *vs* 12.1%, $P=0.0001$).¹³ A sub-analysis of TRITON-TIMI 38 demonstrated that prasugrel reduced the primary end point in the stented cohort, both in the drug-eluting stent (9% *vs* 11.1%, $P=0.019$)¹⁴ and bare metal stent groups (10% *vs* 12.2%, $P=0.003$). However, prasugrel significantly increased major bleeding and fatal bleeding when compared to clopidogrel, especially in elder patients >75 years, patients weighing less than 60 kg and those with a previous stroke or transient ischemic attack.¹³

In a multicenter double-blind randomized controlled trial (RCT), the Study of Platelet Inhibition And Patients Outcomes (PLATO), ticagrelor plus aspirin was compared with clopidogrel plus aspirin in the prevention of CV events in 18 624 patients with ACS. Ticagrelor was found to be superior to clopidogrel in reducing the primary end point of composite death from CV causes, as seen in 9.8% patients receiving ticagrelor *vs* 11.7% receiving clopidogrel ($P<0.001$). No significant difference in major or fatal GI bleeding rates was found between the ticagrelor and clopidogrel groups,¹⁵ although there were higher rates of fatal intracranial bleeding in the ticagrelor group. Based on these data, the American College of Chest Physicians¹⁶ issued a recommendation of low dose aspirin plus either ticagrelor 90 mg twice daily, clopidogrel 75 mg/day or prasugrel 10 mg/day for patients with ACS undergoing PCI with stent placement.

ANTIPLATELET AND GI BLEEDING

1. Antiplatelet drugs increase the risk of GI bleeding

There is no question that antiplatelet therapy is associated with an increased risk of upper GI bleeding.¹⁷ Ibáñez *et al.* showed that the odds ratio (OR) for

upper GI bleeding was 4.0 (3.2–4.9) for patients taking aspirin, 2.3 (0.9–6.0) for those on clopidogrel, 0.9 (0.4–2.0) for those on dipyridamole and 3.1 (1.8–5.1) for those on ticlopidine. A meta-analysis of 18 trials involving 129 314 patients evaluated the bleeding risk of antiplatelet therapy. Not surprisingly, patients on dual antiplatelet therapy were associated with an increased risk of major (RR 1.47, 95% CI 1.36–1.60) and minor bleeding (RR 1.56, 95% CI 1.47–1.66). These patients have a 40–50% increase in risk of major and minor bleeding.¹⁸

2. PPIs are superior to H₂-receptor antagonists (H₂RAs) in primary and secondary prevention of aspirin induced ulcer

Primary prevention

H₂RAs have been shown to be effective as primary prevention for aspirin-induced peptic ulcer disease in average-risk patients. Taha *et al.*¹⁹ conducted a phase III, randomized, double-blind, placebo-controlled trial to assess the effect of famotidine, an H₂RA, on patients receiving aspirin who had no previous peptic ulcers at baseline. At 12 weeks, patients treated with famotidine had a lower incidence of gastric ulcers (3.4% *vs* 15%; OR 0.2, 95% CI 0.09–0.47, *P* = 0.0002), duodenal ulcers (0.5% *vs* 8.5%; OR 0.05, 95% CI 0.01–0.40, *P* = 0.0045) and erosive esophagitis (4.4% *vs* 19%; OR 0.20, 95% CI 0.09–0.42, *P* < 0.0001). This study confirmed the role of H₂RAs as primary prevention in aspirin-induced ulcers.

Similarly, PPIs have also been shown to be effective as primary prevention for aspirin-induced ulcer. Yeomans *et al.*²⁰ assessed the efficacy of esomeprazole for reducing the risk of gastroduodenal ulcers associated with low-dose aspirin for 26 weeks. Peptic ulcer disease developed in 5.4% of the patients treated with placebo compared with 1.6% in the esomeprazole group. There were significantly fewer patients who developed erosive esophagitis in the esomeprazole group (4.4% *vs* 18.3%, *P* < 0.0001).

PPIs were found to be superior to H₂RAs in the primary prevention of peptic ulcer disease, especially in those treated with multiple antiplatelet therapies. Ng *et al.*²¹ conducted an RCT comparing the efficacy of famotidine and esomeprazole in preventing GI complications in patients with ACS or ST-elevation MI receiving aspirin, clopidogrel and enoxaparin or thrombolysis. Significantly more patients presented with upper GI bleeding in the famotidine group than the esomeprazole group (6.1% *vs* 0.6%, *P* = 0.0052).

A retrospective analysis from the same authors²² earlier also demonstrated that the risk of upper GI bleeding was marginally reduced by H₂RAs (OR 0.43, 95% CI 0.18–0.91, *P* = 0.04) and significantly reduced by PPIs (OR 0.04, 95% CI 0.002–0.21, *P* = 0.002).

Secondary prevention

For secondary prevention of aspirin-induced peptic ulcer disease, PPIs again have been shown to be superior to H₂RAs. Bardhan *et al.*²³ studied the efficacy of lansoprazole and ranitidine as a maintenance treatment for 12 months in patients known to have duodenal ulcers and who had been previously treated with either lansoprazole or ranitidine for 8 weeks. Patients treated with lansoprazole achieved a much higher ulcer healing rate than those on ranitidine (98% *vs* 89%, *P* < 0.001) and it provided more rapid symptom relief than ranitidine. For the maintenance phase, lansoprazole was found to be superior to ranitidine in the prevention of relapse (lansoprazole 30 mg, 5% of relapse and lansoprazole 15 mg, 12% of relapse *vs* ranitidine 150 mg, 21% of relapse, respectively). Similarly, Ng *et al.*²⁴ performed a double-blind RCT comparing high-dose famotidine and pantoprazole in preventing recurrent aspirin-related peptic ulcer. Pantoprazole was found to be superior in preventing peptic ulcer bleeding (0% *vs* 7.7%, *P* = 0.0289) and recurrent dyspepsia (0% *vs* 12.3%, *P* = 0.0031).

3. *Helicobacter pylori* (*H. pylori*) detection and eradication is recommended for high GI risk patients before commencing long-term aspirin

4. Continuing PPIs after *H. pylori* eradication is superior to *H. pylori* eradication alone in preventing recurrent ulcer bleeding in patients on aspirin

Several risk factors for GI bleeding have been identified and reported (Table 2),^{25–31} including a prior history of peptic ulcer disease, concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), short-term rather than chronic NSAIDs users, COX-2 inhibitors,³² clopidogrel, anticoagulants,^{33–35} prednisolone^{36,37} or aspirin,^{38,39} *H. pylori* infection and age (>65 years old).^{25,26} Obviously, the more risk factors a patient possesses, the higher the risk of upper GI bleeding. By identifying and eliminating the risk factors the risk of GI bleeding could be minimized.

Chan *et al.*⁴⁰ showed that *H. pylori* eradication was as good as providing PPIs maintenance therapy in

Table 2. Risk factors for upper gastrointestinal (GI) bleeding

Prior history of GI bleeding
Concomitant NSAIDs
Concomitant COX-2 inhibitors
Concomitant anticoagulants
Concomitant clopidogrel
Concomitant corticosteroids
<i>Helicobacter pylori</i> infection
Age >65 years
Short-term NSAIDs

NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase.

patients with a history of upper GI bleeding who were taking aspirin. The probability of recurrent bleeding at 6 months was 1.9% for patients receiving eradication therapy and 0.9% for those receiving omeprazole (absolute difference 1.0%, $P > 0.05$). However, a meta-analysis of six studies revealed that *H. pylori* eradication therapy was superior to anti-secretory non-eradication therapy without subsequent long-term maintenance anti-secretory treatment (4.5% vs 23.7%, OR 0.18, number needed to treat [NNT] 5) in preventing recurrent ulcer bleeding. NNT with eradication therapy to prevent one episode of rebleeding, compared with non-eradication therapy, was 5 (95% CI 4–8) with the fixed effect model. The rebleeding rate for *H. pylori* eradication group was 1.6% vs 5.6% in the maintenance anti-secretory therapy group (OR 0.25, NNT 20).⁴¹ Lai *et al.*⁴² further confirmed that treatment with PPIs following successful *H. pylori* eradication significantly reduces the risk of recurrent ulcer complications. In patients with aspirin-induced ulcer and successful *H. pylori* eradication, lansoprazole maintenance therapy was associated with a lower recurrence rate (1.6% vs 14.8%) than placebo at 12-month follow-up. It is, therefore, worth detecting and eradicating *H. pylori* infection in patients followed by PPIs maintenance in high GI bleeding risk patients who require long-term aspirin, although long-term data are lacking.

5. In patients with previous upper GI bleeding, PPIs should be added to antiplatelet therapy to prevent recurrent ulcer bleeding

Patients who have previous upper GI bleeding from any cause are at a higher risk of recurrence. For patients with aspirin-induced peptic ulcer bleeding and who need to continue with antiplatelet therapy, the initial recommendation was to prescribe clopidogrel to replace aspirin for the prevention of recurrent peptic ulcer. However, subsequent studies have

confirmed that adding PPIs to aspirin was a better approach than replacing aspirin with clopidogrel to prevent recurrent peptic ulcer disease. Doggrel assigned clopidogrel to 161 patients and aspirin plus esomeprazole to 159 patients following endoscopically confirmed ulcer healing. The combination therapy with aspirin and esomeprazole was shown to be superior to clopidogrel alone in preventing recurrent ulcer bleeding (0.6% vs 8.1%, $P < 0.001$).⁴³ This finding was confirmed in an important clinical trial by Chan *et al.*⁴⁴ involving 320 patients, again showing that the combination of aspirin and esomeprazole is superior to switching to clopidogrel (the cumulative incidence of recurrent bleeding at 12 months was 8.6% and 0.7% for those on clopidogrel vs aspirin + esomeprazole, respectively; $P = 0.001$) in preventing recurrent ulcer bleeding. A similar conclusion was drawn by Lai *et al.*⁴⁵ in a different, prospective, double-blind, randomized controlled study involving 170 patients with aspirin-induced ulcer bleeding. The cumulative incidence of recurrent ulcer bleeding was 0% in the aspirin plus esomeprazole group vs 13.6% in the clopidogrel group ($P = 0.0019$).

6. Patients with a high risk for GI bleeding requiring antiplatelet therapy should be on long-term PPIs

Primary prophylaxis for GI bleeding is not necessary for patients with average GI bleeding risk commencing aspirin. In average risk patients starting aspirin therapy, the risk of major upper GI bleeding is increased 1.5 to 3.2 fold and the absolute rate is increased by 0.12% per year. The number needed to harm (NNH) at one year was 833 (95% CI 526–1429).⁴⁶

In patients at high risk of GI bleeding but who have not bled in the past, PPI should be added if they require antiplatelet therapy. RCT on the assessment of the risk of GI event comparing omeprazole vs placebo in patients on dual antiplatelet therapy clearly demonstrated that omeprazole significantly reduced the rate of upper GI bleeding (1.1% vs 2.9%, $P < 0.001$).⁴⁷

PPI-CLOPIDOGREL INTERACTION

1. PPIs inhibit the activation of clopidogrel via the cytochrome P450 (CYP) 2C19 (CYP2C19) pathway, based on *in vitro* studies

Clopidogrel is a prodrug metabolized by the CYP enzyme system to form its active metabolite. PPIs may

diminish the antiplatelet effect of clopidogrel by inhibiting CYP2C19 isoenzyme and therefore the conversion of clopidogrel into its active metabolite. This may explain the adverse clinical outcomes associated with the concomitant use of PPIs and clopidogrel reported previously.⁴⁸

Gilard *et al.*⁴⁹ revealed that omeprazole significantly decreased the clopidogrel inhibitory effect on platelets. This was confirmed by Small *et al.*⁵⁰ and Sibbing *et al.*⁵¹ O'Donoghue *et al.*⁵² measured the platelet function *in vitro* in the presence of clopidogrel and prasugrel and observed an attenuation of the antiplatelet effect. However, this is not associated with adverse clinical outcome, suggesting that surrogate end points should not be used as a substitute for clinical events.

2. There is no consistent evidence that any single particular PPI interacts adversely with clopidogrel

Studies comparing the effect of various PPIs on clopidogrel have yielded inconsistent results. Using platelet reactivity index (PRI) vasoactive stimulated phosphoprotein as a measurement for clopidogrel non-responders, there were significantly more clopidogrel non-responders among patients taking omeprazole than those taking pantoprazole (44% vs 23%, $P = 0.04$, OR 2.6, 95% CI 1.2–6.2) at 1 month when Cuisset *et al.*⁵³ compared the effect of omeprazole and pantoprazole on the platelet response to clopidogrel after coronary stenting in 104 patients. Siller-Matula *et al.*,⁵⁴ however, did not find any difference between pantoprazole and esomeprazole in the mean PRI and platelet aggregation. They concluded that neither esomeprazole nor pantoprazole were associated with an impaired response to clopidogrel. Angiolillo *et al.*⁵⁵ performed four randomized placebo-controlled studies on 282 healthy participants to investigate the potential interaction between omeprazole and clopidogrel and if this existed, whether this effect could be mitigated by separating the dosing to 12 h apart or by increasing the dosage of clopidogrel or substituting omeprazole with pantoprazole. The studies revealed that omeprazole decreased the clopidogrel active metabolite significantly, whether it was given simultaneously, 12 h apart or with higher dosing of clopidogrel. Substituting omeprazole with pantoprazole had the least effect on active clopidogrel metabolites. Similarly Frelinger *et al.*⁵⁶ demonstrated that esomeprazole but not lansoprazole or dexlansoprazole significantly decreased the clopidogrel active metabolite and reduced the effect of clopidogrel on vasodilator-

stimulated phosphoprotein PRI. Kwok and Loke⁵⁸ conducted a systematic review of 19 studies and 4693 patients on the effects of PPIs on platelet functions in patients receiving clopidogrel. Only omeprazole was implicated, whereas pantoprazole and esomeprazole did not demonstrate any significant interaction.⁴⁷

Clinical outcome studies on the PPI–clopidogrel interaction have also been inconsistent. Although observational studies have suggested an interaction between PPI and clopidogrel with adverse clinical outcomes,^{48,59–62} there are also many clinical studies that failed to show a positive association.^{52,63,64} A meta-analysis of 23 studies⁵⁷ involving 93 278 patients demonstrated that PPIs use simultaneously with clopidogrel was not associated with an increase in CV risk, after adjusting for confounders. No one PPI was implicated in this analysis. The only RCT on this topic showed a significant reduction in bleeding peptic ulcer disease in patients given PPIs without an increase in CV events.^{47,58}

H₂RAs had been proposed as a substitute for PPIs in patients on clopidogrel requiring peptic ulcer disease bleeding prophylaxis. A population-based retrospective cohort study⁶⁵ of 6552 patients in Taiwan, China showed that both PPIs and H₂RAs were independent risk factors for adverse outcomes. The risk of rehospitalization for ACS or all-cause mortality within 3 months of rehospitalization was 26.8% (95% CI 21.5–33.0%, NNH = 7) in the clopidogrel plus H₂RA cohort and 33.2% (95% CI 27.8–39.4%, NNH = 5) in the clopidogrel plus PPI cohort, compared with 11.6% (95% CI 10.8–12.5%) in the clopidogrel alone cohort ($P < 0.0001$). In contrast, Tungal *et al.*⁶⁶ demonstrated that neither esomeprazole nor famotidine reduced the platelet inhibitory effect of clopidogrel based on platelet reactivity units at baseline and at day 28. There has also been no clinical evidence to demonstrate that H₂RAs are effective in preventing peptic ulcer complications in patients taking clopidogrel.

Obviously, if there is any doubt, prasugrel^{50,66} and ticagrelor^{68–70} are an alternative as neither has been shown to have any significant interactions with PPIs. In an analysis of two RCTs to assess the pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel in the presence of PPIs, O'Donoghue *et al.*⁵² demonstrated that the mean inhibition of platelet aggregation was significantly lower for patients on PPIs than those without after clopidogrel treatment ($23.2\% \pm 19.5\%$ vs $35.2\% \pm 20.9\%$, $P = 0.02$), whereas a more modest difference was found after

prasugrel was given ($69.6\% \pm 13.5\%$ vs $76.7\% \pm 12.4\%$, $P = 0.054$). In the TRITON-TIMI 38 trial¹³ to assess clinical efficacy, PPIs use was not associated with any CV risk in patients treated with clopidogrel (adjusted hazard ratio [HR] 0.94, 95% CI 0.80–1.11) or prasugrel (adjusted HR 1.00, 95% CI 0.84–1.20).

Similarly, Storey *et al.*⁷⁰ demonstrated that ticagrelor has a greater antiplatelet inhibitory effect than clopidogrel and the concomitant use of PPIs did not have any effect on ticagrelor. Goodman *et al.*⁶⁸ examined the relationship between PPIs use and 1-year CV events in patients with ACS receiving either clopidogrel or ticagrelor. Patients treated with PPIs had a higher risk of CV end points, both in the clopidogrel and ticagrelor group. A similar trend was found in patients taking other non-PPI GI drugs. However, patients without any gastric therapy had a significantly lower level of CV events (PPIs vs no GI treatment: clopidogrel, HR 1.29, 95% CI 1.12–1.49; ticagrelor, HR 1.30, 95% CI 1.14–1.49). The authors concluded that PPIs use was a marker, and not the cause, of a higher rate of CV events in the PLATO trial.

RECOMMENCING ANTIPLATELET THERAPY FOLLOWING BLEEDING

1. Aspirin should be recommended early to reduce CV mortality although it increases the risk of GI bleeding

The decision to continue with antiplatelet therapy remains a clinical challenge, especially in those who need to continue their antiplatelet therapy due to a recent MI, and post-PCI with stent implantation. Obviously, the initial step is to assess whether antiplatelet therapy is still required. If there is a continuous need, then following endoscopic therapy for GI bleeding the endoscopist will have to decide if continuing antiplatelet therapy is possible. If hemostasis is achieved and the risk of rebleeding is low, then antiplatelet therapy could be resumed immediately. At present, there are no published data to recommend the ideal timing to restart antiplatelet therapy. In patients at high risk of recurrent bleeding, resuming antiplatelet therapy between days 3–5 is a reasonable approach, as most recurrent ulcer bleeding occur within 72 h and the half-life of antiplatelet agents is 5–7 days.

Adherence to aspirin in a non-acute situation was associated with a significant reduction in MI.⁷¹ Similarly, Rodriguez *et al.*⁷² confirmed that poor compliance with aspirin among patients with coronary heart

disease was significantly associated with a higher rate of MI. In a meta-analysis Biondi-Zoccai *et al.*⁷³ revealed that aspirin non-adherence or withdrawal was associated with a threefold increase risk of major adverse cardiac events. This risk was even higher in patients with intracoronary stents (OR 89.78). In a randomized placebo-controlled trial, Sung *et al.*⁷⁴ assessed the risk of recurrent bleeding and CV mortality in patients who continue to receive aspirin with PPIs following endoscopic therapy to control peptic ulcer bleeding. Continuous aspirin therapy was associated with a higher risk of recurrent ulcer bleeding but lower mortality. Peptic ulcer healing was not affected by the continuation of aspirin once PPI is started. The peptic ulcer healing rate is similar in patients treated with PPIs alone or PPIs plus aspirin.⁷⁵

In conclusion, antiplatelet drugs are the cornerstone in the management of CV diseases but they are associated with the risk of GI bleeding. A prior history of peptic ulcer bleeding or other complications are the strongest risk factors and predictors for the subsequent peptic ulcer bleeding. PPIs co-prescription in the high-risk group is associated with a reduced risk of GI bleeding in patients requiring antiplatelet therapy. Data on clopidogrel–PPI interactions are inconclusive and PPIs should be considered after balancing the CV risk and GI complications in patients treated with clopidogrel, especially in combination with aspirin and other risk factors. Newer antiplatelet agents are suitable alternatives, as they have not been shown to have any significant interactions with PPIs. The early commencement of antiplatelet agent following GI bleeding has been shown to reduce CV mortality, despite the risk of increases in recurrent bleeding.

ACKNOWLEDGMENT

This project was supported by an unrestricted educational grant from Astra Zeneca.

REFERENCES

- 1 Hankey GJ, Eikelboom JW. Antiplatelet drugs. *Med J Aust* 2003; 178:568–74.
- 2 Ridker PM, Cook NR, Lee IM *et al.* A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005; 352: 1293–304.
- 3 Hankey GJ, Sudlow CL, Dunbabin DW. Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. *Cochrane Database Syst Rev* 2000; (2): CD001246.
- 4 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348: 1329–39.

- 5 Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345: 494–502.
- 6 Keller TT, Squizzato A, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2007; (3): CD005158.
- 7 Squizzato A, Keller T, Romualdi E, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2011; (1): CD005158.
- 8 Chen ZM, Jiang LX, Chen YP *et al*; COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; 366: 1607–21.
- 9 Sabatine MS, Cannon CP, Gibson CM *et al*; CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; 352: 1179–89.
- 10 Berger PB, Bhatt DL, Fuster V *et al*; CHARISMA Investigators. Bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Circulation* 2010; 121: 2575–83.
- 11 Mehta SR, Yusuf S, Peters RJ *et al*; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. 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.
- 12 Steinhubl SR, Berger PB, Mann JT 3rd *et al*; CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; 288: 2411–20.
- 13 Wiviott SD, Braunwald E, McCabe CH *et al*; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; 357: 2001–15.
- 14 Wiviott SD, Braunwald E, McCabe CH *et al*; TRITON-TIMI 38 Investigators. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet* 2008; 371: 1353–63.
- 15 Wallentin L, Becker RC, Budaj A *et al*; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361: 1045–57.
- 16 Vandvik PO, Lincoff AM, Gore JM *et al*; American College of Chest Physicians. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e637S–68S.
- 17 Ibáñez L, Vidal X, Vendrell L, Moretti U, Laporte JR; Spanish-Italian Collaborative Group for the Epidemiology of Gastrointestinal Bleeding. Upper gastrointestinal bleeding associated with antiplatelet drugs. *Aliment Pharmacol Ther* 2006; 23: 235–42.
- 18 Serebrnyy VL, Malinin AI, Ferguson JJ, Vahabi J, Atar D, Hennekens CH. Bleeding risks of combination vs single antiplatelet therapy: a meta-analysis of 18 randomized trials comprising 129,314 patients. *Fundam Clin Pharmacol* 2008; 22: 315–21.
- 19 Taha AS, McCloskey C, Prasad R, Bezlyak V. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 374: 119–25.
- 20 Yeomans N, Lanas A, Labenz J *et al*. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. *Am J Gastroenterol* 2008; 103: 2465–73.
- 21 Ng F, Tungal P, Chu WM *et al*. Esomeprazole compared with famotidine in the prevention of upper gastrointestinal bleeding in patients with acute coronary syndrome or myocardial infarction. *Am J Gastroenterol* 2012; 107: 389–96.
- 22 Ng FH, Lam KF, Wong SY *et al*. Upper gastrointestinal bleeding in patients with aspirin and clopidogrel co-therapy. *Digestion* 2008; 77: 173–7.
- 23 Bardhan KD, Crowe J, Thompson RP *et al*. Lansoprazole is superior to ranitidine as maintenance treatment for the prevention of duodenal ulcer relapse. *Aliment Pharmacol Ther* 1999; 13: 827–32.
- 24 Ng FH, Wong SY, Lam KF *et al*. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. *Gastroenterology* 2010; 138: 82–8.
- 25 Almadi MA, Barkun A, Brophy J. Antiplatelet and anticoagulant therapy in patients with gastrointestinal bleeding: an 86-year-old woman with peptic ulcer disease. *JAMA* 2011; 306: 2367–74.
- 26 Laine L. Review article: gastrointestinal bleeding with low dose aspirin – what's the risk? *Aliment Pharmacol Ther* 2006; 24: 897–908.
- 27 Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 2009; 104: 728–38.
- 28 Fries JF, Williams CA, Bloch DA, Michel BA. Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models. *Am J Med* 1991; 91: 213–22.
- 29 Silverstein FE, Graham DY, Senior JR *et al*. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; 123: 241–9.
- 30 Lanas A, Bajador E, Serrano P *et al*. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. *N Engl J Med* 2000; 343: 834–9.
- 31 Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. *Aliment Pharmacol Ther* 2002; 16: 1945–53.
- 32 Schnitzer TJ, Burmester GR, Mysler E *et al*; TARGET Study Group. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004; 364: 665–74.
- 33 Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002; 347: 969–74.
- 34 Johnson WC, Williford WO; Department of Veterans Affairs Cooperative Study. Benefits, morbidity, and mortality

- associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. *J Vasc Surg* 2002; 35: 413–21.
- 35 Gulløv AL, Koefoed BG, Petersen P. Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation: the AFASAK 2 study. Atrial fibrillation aspirin and anticoagulation. *Arch Intern Med* 1999; 159: 1322–8.
 - 36 Nielsen GL, Sørensen HT, Møllekjær L *et al*. Risk of hospitalization resulting from upper gastrointestinal bleeding among patients taking corticosteroids: a register-based cohort study. *Am J Med* 2001; 111: 541–5.
 - 37 Sørensen HT, Møllekjær L, Blot WJ *et al*. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol* 2000; 95: 2218–24.
 - 38 Hansson L, Zanchetti A, Carruthers SG *et al*; HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; 351: 1755–62.
 - 39 Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005; 353: 2373–83.
 - 40 Chan FK, Chung SC, Suen BY *et al*. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med* 2001; 344: 967–73.
 - 41 Gisbert JP, Khorrami S, Carballo F, Calvert X, Gene E, Dominguez-Muñoz E. Meta-analysis: *Helicobacter pylori* eradication therapy vs antisecretory non-eradication therapy for the prevention of recurrent bleeding from peptic ulcer. *Aliment Pharmacol Ther* 2004; 19: 617–29.
 - 42 Lai KC, Lam SK, Chu KM *et al*. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002; 346: 2033–8.
 - 43 Doggrell SA. Aspirin and esomeprazole are superior to clopidogrel in preventing recurrent ulcer bleeding. *Expert Opin Pharmacother* 2005; 6: 1253–6.
 - 44 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.
 - 45 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.
 - 46 McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006; 119: 624–38.
 - 47 Bhatt DL, Cryer BL, Contant CF *et al*; COGENT Investigators. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010; 363:1909–17.
 - 48 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: 713–8.
 - 49 Gilard M, Arnaud B, Cornily JC *et al*. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008; 51: 256–60.
 - 50 Small DS, Farid NA, Payne CD *et al*. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. *J Clin Pharmacol* 2008; 48: 475–84.
 - 51 Sibbing D, Morath T, Stegheer J *et al*. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. *Thromb Haemost* 2009; 101: 714–9.
 - 52 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.
 - 53 Cuisset T, Frere C, Quilici J *et al*. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose: the PACA (Proton Pump Inhibitors And Clopidogrel Association) prospective randomized study. *J Am Coll Cardiol* 2009; 54: 1149–53.
 - 54 Siller-Matula JM, Spiel AO, Lang IM, Kreiner G, Christ G, Jilma B. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. *Am Heart J* 2009; 157: 148.e1–5.
 - 55 Angiolillo DJ, Gibson CM, Cheng S *et al*. Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies. *Clin Pharmacol Ther* 2011; 89: 65–74.
 - 56 Frelinger AL 3rd, Lee RD, Mulford DJ *et al*. A randomized, 2-period, crossover design study to assess the effects of dexlansoprazole, lansoprazole, esomeprazole and omeprazole on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers. *J Am Coll Cardiol* 2012; 59: 1304–11.
 - 57 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.
 - 58 Kwok CS, Loke YK. Effects of proton pump inhibitors on platelet function in patients receiving clopidogrel: a systematic review. *Drug Saf* 2012; 35: 127–39.
 - 59 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.
 - 60 Aubert RE, Epstein RS, Teagarden JR *et al*. Proton pump inhibitors effect on clopidogrel effectiveness: the clopidogrel Medco outcome study. *Circulation* 2008; 118: S_815.
 - 61 Gupta E, Bansal D, Sotos J, Olden K. Risk of adverse clinical outcomes with concomitant use of clopidogrel and proton pump inhibitors following percutaneous coronary intervention. *Dig Dis Sci* 2010; 55: 1964–8.
 - 62 van Boxel OS, van Oijen MG, Hagens MP, Smout AJ, Siersema PD. Cardiovascular and gastrointestinal outcomes in clopidogrel users on proton pump inhibitors: results of a large Dutch cohort study. *Am J Gastroenterol* 2010; 105: 2430–6; quiz 2437.
 - 63 Ramirez JF, Selzer F, Chakrapani R *et al*. Proton pump inhibitor and clopidogrel combination is not associated with adverse clinical outcomes after PCI: the NHLBI dynamic registry. *J Am Coll Cardiol* 2009; 53: A27.
 - 64 Simon T, Verstuyft C, Mary-Krause M *et al*; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009; 360: 363–75.
 - 65 Wu CY, Chan FK, Wu MS *et al*. Histamine2-receptor antagonists are an alternative to proton pump inhibitor in patients receiving clopidogrel. *Gastroenterology* 2010; 139: 1165–71.
 - 66 Tunggal P, Ng FH, Lam KF, Chan FK, Lau YK. Effect of esomeprazole versus famotidine on platelet inhibition by

- clopidogrel: a double-blind, randomized trial. *Am Heart J* 2011; **162**: 870–4.
- 67 Aradi D, Kuliczkowski W, Atar D, Serebruany VL. Inter-patient variability and impact of proton pump inhibitors on platelet reactivity after prasugrel. *Thromb Haemost* 2012; **107**: 338–45.
- 68 Goodman SG, Clare R, Pieper KS *et al*; Platelet Inhibition and Patient Outcomes Trial Investigators. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes trial. *Circulation* 2012; **125**: 978–86.
- 69 Thomas MR, Storey RF. Optimal management of antiplatelet therapy and proton pump inhibition following percutaneous coronary intervention. *Curr Treat Options Cardiovasc Med* 2012; **14**: 24–38.
- 70 Storey RF, Angiolillo DJ, Patil SB *et al*. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATElet inhibition and patient Outcomes) PLATELET substudy. *J Am Coll Cardiol* 2010; **56**: 1456–62.
- 71 Glynn RJ, Buring JE, Manson JE, LaMotte F, Hennekens CH. Adherence to aspirin in the prevention of myocardial infarction. The Physicians' Health Study. *Arch Intern Med* 1994; **154**: 2649–57.
- 72 Rodriguez LA, Cea-Soriano L, Martín-Merino E, Johansson S. Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. *BMJ* 2011; **343**: d4094.
- 73 Biondi-Zoccai GG, Lotrionte M, Agostoni P *et al*. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J* 2006; **27**: 2667–74.
- 74 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.
- 75 Liu CP, Chen WC, Lai KH *et al*. Esomeprazole alone compared with esomeprazole plus aspirin for the treatment of aspirin-related peptic ulcers. *Am J Gastroenterol* 2012; **107**: 1022–9.