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Anti-platelet therapy and managing ulcer risk

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Abstract

Low-dose aspirin (ASA) has emerged as one of the most important causes of peptic ulcer bleeding in developed countries. Among the risk factors of ASA-associated ulcer bleeding, *Helicobacter pylori* infection is one of the few that is treatable. Recent evidence showed that among patients with a history of ASA-associated ulcer bleeding, the long-term incidence of recurrent bleeding with ASA use is low after eradication of *H. pylori* alone. Thus, test-and-treat *H. pylori* is a potentially useful strategy for ASA users with high ulcer risk. However, the risk of bleeding is further increased by combining other anti-platelet drugs (e.g. clopidogrel) with ASA in acute coronary syndromes and coronary stent placement. There is good evidence that co-therapy with a proton-pump inhibitor (PPI) reduces upper gastrointestinal bleeding with ASA alone or dual anti-platelet therapy. Recently, several meta-analyses of observational studies found that concurrent use of PPI and clopidogrel was associated with increased risk of major adverse cardiovascular events. Overall, the evidence does not suggest a clinically important interaction between PPIs and clopidogrel. However, there is a subset of patients who have reduced conversion of clopidogrel to its active metabolites due to genetic polymorphism of hepatic P-450 (carriers of CYP2C19 loss-of-function alleles). Since PPIs are also metabolized by similar hepatic enzymes, it is uncertain whether patients carrying CY2C19 loss-of-function alleles are susceptible to concomitant PPI use. In the future, management of patients on dual anti-platelet therapy needs to be individualized according to their thrombotic and bleeding risks.

Introduction

Over the last two decades, upper gastrointestinal (GI) bleeding associated with low-dose aspirin (ASA) has been rising rapidly. In Scotland, hospitalizations for ASA-associated upper GI bleeding have increased from 15 patients per 100 000 in 1996 to nearly 40 patients per 100 000 in 2005.[1] Since many patients require lifelong ASA for prevention of atherothrombotic diseases, identifying patients at risk of upper GI bleeding and developing cost-effective strategies for reducing the bleeding risk is an important healthcare issue. However, management of patients on anti-platelet therapy becomes more complicated for several reasons.

First, patients undergoing percutaneous coronary intervention such as coronary stent placement often require complex anti-platelet and anti-thrombotic therapy. These patients not only are at increased risk of GI bleeding but also coronary thrombosis. Balancing the bleeding and thrombotic risks of individual patients is a major clinical challenge.

Second, recent evidence suggests that concurrent use of proton-pump inhibitor (PPI) and clopidogrel increases the risk of major adverse cardiovascular events such as myocardial infarction. Currently, health authorities in the U.S. and in Europe have issued warnings against the use of PPIs in patients receiving clopidogrel. Whether these warnings are appropriate or clinically helpful remain controversial.

Third, there is a lack of practical guidelines on balancing bleeding and thrombotic risks in patients on anti-platelet therapy. This lecture aims to address the above issues and provides an overview of managing patients on anti-platelet therapy who are at risk of bleeding and thrombosis.

Risk factors for ASA-associated upper GI bleeding

A number of risk factors for upper GI bleeding with ASA have been consistently reported. These include history of ulcer bleeding, dose of ASA, advanced age (> 70), concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), and *Helicobacter pylori* infection.[2–4] Among survivors of myocardial infarction, a 24-month prospective study found that the incidence of serious GI bleeding was very high during the first 2 months (cumulative incidence: 0.13% up to Month 2 versus 0.018% from Month 3 to

Month 24). On multivariate analysis, additional risk factors for GI bleeding include use of dual anti-platelet therapy (hazard ratio [HR] 3.18, 95% confidence interval [CI], 1.91–5.29), concomitant anti-coagulants (HR 2.13, 95% CI, 1.28–3.52), history of alcohol abuse (HR 4.71, 95% CI, 2.02–11.01), New York Heart Association class III or IV (HR 2.27, 95% CI, 1.28–3.52), diabetes (HR 1.76, 95% CI, 1.13–2.74), renal failure (HR 1.18, 95% CI, 1.03–1.34), and non-white race (HR 3.26, 95% CI, 1.89–5.61).[5]

Strategies for reducing upper GI bleeding with ASA

Patients receiving ASA should be evaluated for the presence of risk factors for peptic ulcer bleeding. Current strategies for reducing upper GI bleeding in high-risk ASA users include avoidance or elimination of risk factors and co-therapy with a gastroprotective agent. However, most of the risk factors cannot be eliminated; *H. pylori* infection is a notable exception.

Can eradication of *H. pylori* reduce the risk of upper GI bleeding with ASA?

Although *H. pylori* is a recognized risk factor for upper GI bleeding in ASA users, whether eradication of *H. pylori* can substantially reduce the risk of bleeding remains unclear. In a 6-month randomized trial, ASA users with *H. pylori* infection and previous ulcer bleeding were randomized to eradication therapy alone or maintenance treatment with a proton-pump inhibitor (PPI). Recurrent ulcer bleeding occurred in 1.9% (95% CI, –0.7%, 4.5%) of patients in the eradication therapy group compared with 0.9% (95% CI, –0.8%, 2.6%) in the PPI group.[6] In another 12-month randomized trial, ASA users with *H. pylori* infection and previous ulcer bleeding were randomized to eradication therapy alone or eradication therapy followed by maintenance PPI. Recurrent ulcer bleeding occurred in 15% (95% CI, 7%, 26%) in the eradication therapy group compared with 1.6% (95% CI, 0%, 9%) in the eradication therapy plus PPI group. Although the latter study found that the rate of recurrent bleeding was unacceptably high with eradication of *H. pylori* alone in high-risk ASA users, the majority of these patients with recurrent bleeding had failure of eradication or used concomitant NSAIDs.[7]

Recently, a 10-year prospective cohort study reported the long-term incidence of ulcer bleeding in three cohorts of ASA users. The first cohort consisted of ASA users with previous ulcer bleeding and confirmed eradication of *H. pylori* (*H. pylori*-eradicated cohort). The second cohort consisted of ASA users with previous ulcer bleeding but no evidence of current or past *H. pylori* infection (*H. pylori*-negative cohort). The third cohort consisted of asymptomatic ASA users without a history of ulcer or ulcer bleeding (average-risk cohort). The rate of ulcer bleeding was 1.08 per 100 patient-years in the *H. pylori*-eradicated cohort (95% CI 0.96, 1.96), 5.77 per 100 patient-years in the *H. pylori*-negative cohort (95% CI 3.46, 9.64), and 0.66 per 100 patient-years in the average-risk cohort (95% CI 0.41, 1.05).[8] These findings suggest that among ASA users with a history of ulcer bleeding, the long-term risk of ulcer bleeding is low after eradication of *H. pylori* alone. Further studies are needed to determine whether test-and-treat *H. pylori* is a cost-effective strategy for reducing ulcer bleeding in high-risk ASA users.

Co-therapy with gastroprotective agents

In addition to modifying the underlying risk factors, ASA users with high risk of ulcer bleeding should receive cotherapy with a gastroprotective agent. For many years, however, the American College of Cardiology and the American Heart Association recommended clopidogrel as an alternative to ASA in patients with major GI intolerance.[9] In a 12-month, double-blind randomized trial of ASA plus esomeprazole versus clopidogrel alone in patients with previous ulcer bleeding who had healed ulcers and negative tests for *H. pylori*, recurrent ulcer bleeding occurred in 0.7% (95% CI, 0%, 2.0%) of patients in the ASA plus esomeprazole group compared with 8.6% (95% CI, 4.1%, 13.1%) in the clopidogrel group ($P = 0.001$).[10] In 2008, a joint expert consensus report of the American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG), and American Heart Association (AHA) stated that substitution of clopidogrel for ASA is not a recommended strategy to reduce the risk of recurrent ulcer bleeding in high-risk patients and is inferior to the combination of ASA plus PPI.[11]

What is the risk of GI bleeding with dual anti-platelet therapy?

With increasing use of dual anti-platelet therapy in patients with coronary stents, not only the incidence but also the complexity of GI bleeding is expected to increase. However, the risk of bleeding with dual anti-platelet therapy is largely derived from secondary analysis of safety data in major clinical trials. In the CURE trial of dual anti-platelet therapy for acute coronary syndromes, adding clopidogrel to aspirin increases the relative risk of GI bleeding by over 85% (1.3% *vs* 0.7% in 12 months).[12] In another trial of dual anti-platelet therapy for atrial fibrillation, major GI bleeding occurred in 1.1%/year of patients receiving dual anti-platelet therapy compared with 0.5%/year in patients receiving aspirin ($P < 0.001$).[13]

Preventing upper GI bleeding with dual anti-platelet therapy

Prevention of GI bleeding associated with dual anti-platelet therapy is important not only because of its widespread use in patients with coronary artery diseases but also due to the thrombotic risk associated with major bleeding. In 2008, a joint consensus report of ACCF/ACG/AHA recommended routine use of prophylactic PPI in patients receiving dual anti-platelet therapy.[11] Subsequently, the efficacy of PPIs in preventing upper GI bleeding associated with dual anti-platelet therapy was confirmed by a double-blind randomized trial. In this study, over 3700 patients with an indication for dual anti-platelet therapy were randomly assigned to receive clopidogrel in combination with either omeprazole or placebo. The primary GI end point was a composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation. The event rate was 1.1% with omeprazole and 2.9% with placebo in 180 days (HR with omeprazole, 0.34, 95% CI, 0.18 to 0.63; $P < 0.001$). The rate of overt upper GI bleeding was also reduced with omeprazole as compared with placebo (HR, 0.13; 95% CI, 0.03 to 0.56; $P = 0.001$).[14]

Can histamine-2-receptor antagonists (H2RAs) reduce upper GI bleeding with dual anti-platelet therapy? To date, there is only one retrospective study that assessed the effect of H2RAs on the risk of upper GI bleeding in patients on dual anti-platelet therapy. After a median follow-up of 5.8 months, upper GI bleeding occurred in 3.14% in the H2RA group ($n = 287$) and 5.95% in the control group ($n = 487$). Thus, the benefit of H2RA is only marginal (O.R. 0.43, 95% CI, 0.18–0.91; $P = 0.04$).[15]

Interaction between PPI and clopidogrel: is the problem overstated?

Although the joint consensus report of the ACCF/ACG/AHA in 2008 recommended routine prophylaxis with a PPI in patients requiring dual anti-platelet therapy, subsequent observational data found that patients receiving concomitant PPI and clopidogrel had significantly higher risk of major cardiovascular adverse events including death, myocardial infarction, stroke, and urgent revascularization.[16,17] Pharmacodynamic interaction exists between PPIs and clopidogrel because both drugs share similar metabolic pathways in the liver. Clopidogrel is a prodrug that requires conversion by hepatic cytochrome P450 isoforms, notably CYP2C19, into active metabolites. These active metabolites then irreversibly antagonize the adenosine diphosphate receptor on platelets. On the other hand, proton-pump inhibitors are prodrugs that are also bioactivated by CYP2C19. PPIs compete with clopidogrel for CYP2C19, thereby reducing conversion of clopidogrel to active metabolites for platelet inhibition.[18] The negative impact of PPIs on the platelet inhibitory effect of clopidogrel has been confirmed by double-blind randomized trials using platelet reactivity index as the study endpoint.[19] *In vitro* studies found that different PPIs have different degrees of inhibitory effects on clopidogrel. Omeprazole and lansoprazole have the strongest inhibitory effect, whereas pantoprazole and rabeprazole are the weakest.[20] Whether there is a good correlation between *in vitro* findings and clinical outcome remains controversial.

In a meta-analysis of cardiovascular outcomes in patients receiving clopidogrel with or without concomitant PPI, there was a significant increase in the risk of myocardial infarction in patients receiving concomitant PPI (risk ratio 1.43, 95% CI, 1.16–1.77).[21] However, substantial heterogeneity was detected. On subgroup analysis, observational studies showed a significant association (risk ratio 1.54, 95% CI, 1.23–1.92) whereas data from randomized trial or propensity-matched participants showed no such association (risk ratio 1.15, 95% CI, 0.89–1.48).

How to account for these inconsistent data? In observational studies, patients receiving concomitant PPIs were older and had more severe concurrent illnesses than patients receiving clopidogrel alone. It is likely that PPIs were more often prescribed to patients with high GI risk or those with anticipated high cardiovascular mortality should bleeding complication develop. Thus, concomitant PPI may be a surrogate marker for, rather than a cause of, serious cardiovascular events among clopidogrel users. When baseline imbalance between patients with and without concomitant PPI use was eliminated in randomized trials, PPI use was not associated with increased incidence of major adverse cardiovascular events.

To date, there is only one double-blind randomized trial that was designed to determine whether concomitant PPI use would adversely affect the cardiovascular outcome of patients on clopidogrel. Patients with an indication for dual anti-platelet therapy were randomly assigned to receive clopidogrel in combination with either omeprazole or placebo. The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, revascularization, or stroke. The study planned to enroll 5000 patients, and 3873 were randomized. The event rates were 4.9% with omeprazole and 5.7% with placebo (H.R. with omeprazole, 0.99; 95% CI, 0.68–1.44; $P = 0.96$). Unfortunately, the trial was terminated prematurely when the sponsor lost financing.[14] Because of premature termination, this study was not powered to detect a small difference in the primary cardiovascular endpoint.

Despite the inconsistent data, the Food and Drug Administration in the U.S. issued a warning in November 2009 that "healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI in patients taking clopidogrel," and that "concomitant use of drugs that inhibit CYP2C19 (e.g. omeprazole) should be discouraged."[22] The European Medicines Agency adopts a more conservative standpoint and "discourages concomitant use of PPI and clopidogrel-containing drugs unless absolutely necessary."[23]

While the overall evidence does not suggest a clinically important interaction between PPIs and clopidogrel for most patients, it remains uncertain as to whether there are certain subgroups of patients who are at risk of this drug interaction. Recently, another meta-analysis of 23 studies also found that patients who are on concurrent PPI and clopidogrel are at higher risk of major adverse cardiovascular events (odds ratio (OR) 1.41, 95% CI, 1.34–1.48, $P < 0.001$).[24] Statistical testing for heterogeneity was again significant for the analysis ($P = 0.001$). Differences between trials in terms of how elements of the composite endpoint were recorded, together with the unintentional inclusion of CYP2C19 genetic polymorphism in the PPI studies may explain why the variability between trials is higher than what can be expected from chance alone. Interestingly, secondary analysis found that underlying high cardiovascular risk (defined as an annual rate of major adverse cardiovascular events > 10%) was the only factor that predicted serious cardiovascular outcomes with concurrent use of PPI and clopidogrel. If this observation is confirmed by prospective trials, we may need to evaluate the cardiovascular risk of patients on clopidogrel before prescribing PPI in the future.

Another uncertainty is whether clopidogrel users with CYP2C19 loss-of-function alleles using concomitant PPIs are at increased risk of serious cardiovascular events. Recent studies reported that certain genetic variants of hepatic cytochrome P-450 system that are involved in the conversion of clopidogrel into its active metabolites are associated with increased risk of recurrent cardiovascular events.[18,25,26] In particular, patients who carry CYP2C19 loss-of-function alleles have reduced conversion of clopidogrel to its active metabolites, leading to decreased platelet inhibition. In a meta-analysis of cardiovascular events according to the genetic variants of CYP2C19, it was found that carriers of the CYP2C loss-of-function alleles (CYP2C19*2) showed a significant increased risk of major adverse cardiovascular events compared with noncarriers (9.7% *vs* 7.8%; OR, 1.29; 95% CI, 1.12–1.49; $P < 0.001$). This genetic variant was also associated with an excess of mortality (1.8% *vs* 1.0%; OR, 1.79; 95% CI, 1.10–2.91; $P = 0.019$) and of stent thrombosis (2.9% *vs* 0.9%; OR, 3.45; 95% CI, 2.14–5.57; $P < 0.001$).[24]

Table 1 Risk factors for coronary stent thrombosis (modified from Becker *et al.*[30])

Clinical risk factors
1. History of stent thrombosis†
2. Acute coronary syndrome or ST-segment elevation myocardial infarction
3. Diffuse coronary artery disease
4. Diabetes mellitus
5. Renal failure
6. Depressed ejection fraction
Procedural risk factors
1. Multi-vessel PCI
2. Multiple stents
3. Coronary dissection
4. Bifurcation stents
Reduced responsiveness to clopidogrel
1. CYP2C19 genetic polymorphism

†History of stent thrombosis is the most important risk factor.

Since patients carrying CYP2C19*2 alleles (i.e. poor metabolizers) will have reduced platelet inhibitory effect with clopidogrel, will concomitant PPI use increase their risk of recurrent cardiovascular events by further reducing the conversion of clopidogrel to its active metabolites? This question is particularly relevant to Asia because the prevalence of carriers of CYP2C19 loss-of-function alleles is between 15% and 25% in Chinese, Japanese and Thai, whereas it is less than 5% in Caucasians.[27,28] To date, there is only one study providing indirect data on the interaction between PPI use and CYP2C19 loss-of-function alleles. In a large-scale French registry of acute myocardial infarction, subgroup analysis of propensity-matched cohorts found that the rate of in-hospital death, recurrent myocardial infarction, or stroke among clopidogrel users with two loss-of function alleles (homozygotes) was 5% and 12% with and without concomitant PPI, respectively. Despite a more than twofold difference in the event rates, the difference did not reach statistical significance (OR, 1.05, 95% CI, 0.03–34.6) because of the small number of patients involved ($n = 44$).[29]

Overall, current evidence suggests that concomitant PPI use does not increase the risk of major adverse cardiovascular events in patients on clopidogrel. However, the safety of PPI in patients with high baseline cardiothrombotic risk and those carrying CYP2C19 loss-of-function alleles (15–25% of Asians) remain to be explored.

Balancing bleeding and thrombotic risks: My personal view

With increasing complexity of anti-platelet therapy for patients undergoing coronary intervention (e.g. intracoronary placement of drug-eluting stents), the management of these patients requires not only careful assessment of the risk of GI bleeding but also the risk of thrombosis. While gastroenterologists are well aware of the risk of bleeding with anti-platelet therapy, many are not familiar with assessing the cardiothrombotic risk of patients with coronary artery disease. Specifically, patients with coronary stents are at high risk of thrombosis. It is therefore important for gastroenterologists to be able to recognize the cardiothrombotic risk factors associated with coronary stents (Table 1) and communicate with cardiologists to optimize the use of anti-ulcer therapy for individual patients.

Table 2 Balancing bleeding and thrombotic risks in patients with coronary stents

	Low thrombotic risk	High thrombotic risk†
Low bleeding risk	No PPI prophylaxis Standard dual anti-platelet therapy	Avoid PPI High-dose clopidogrel?? Alternative anti-platelet therapy (Prasugrel/Ticagrelor)
High bleeding risk	PPI prophylaxis, Standard dual anti-platelet therapy	Stagger the administration of PPI and clopidogrel (12 h apart) Avoid omeprazole Alternative anti-platelet therapy

†High thrombotic risk. 1. Clinical/procedural risk factors for stent thrombosis; 2. Genetic testing for CYP2C19 loss-of-function alleles; 3. Platelet reactivity test (PRU ≥ 230, VerifyNow P2Y12 assay).

In future, we should no longer focus on managing the ulcer risk of patients on anti-platelet therapy. Instead, we should aim at developing individualized therapy to balance bleeding and thrombotic risks. Patients with high thrombotic risk, e.g. a history of stent thrombosis or multiple clinical/procedural risk factors (Table 2) should undergo laboratory tests for reduced responsiveness to clopidogrel. Commercially available tests include platelet reactivity test (e.g. VerifyNow® P2Y12 assay: cut-off at PRU ≥ 230) and genetic test for CYP2C19 loss-of-function alleles. Patients with high thrombotic risk and low bleeding risk should avoid using PPI.

High-dose clopidogrel has been advocated to overcome patients with high on-treatment platelet reactivity. However, recent studies found that high-dose clopidogrel was not effective in overcoming poor response to clopidogrel in CYP2C19*2 allele carriers.[31] In another randomized trial, high-dose clopidogrel compared with standard-dose clopidogrel did not reduce cardiovascular deaths, nonfatal myocardial infarction, or stent thrombosis in patients with high on-treatment reactivity after placement of drug-eluting stents.[32] Current evidence suggests that prasugrel, a new platelet P2Y12-ADP receptor antagonist, is more effective than high-dose clopidogrel in inhibiting platelet reactivity in patients with high on-treatment platelet reactivity following long-term clopidogrel therapy.[33]

Patients with high bleeding and thrombotic risks require PPI prophylaxis. Because of the concern about PPI-clopidogrel interaction, one potential (though unproven) strategy is to stagger the administration of these drugs 12 h apart. This approach can probably avoid the drug interaction, if any, because the elimination half life of PPIs is only about 1–1.5 h and that of clopidogrel is 4–6 h. One should avoid using omeprazole because it has the strongest inhibitory effect on CYP2C19. Alternatively, new anti-platelet drugs such as prasugrel ot ticagrelor may be considered.

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