Is There an Optimal Antiplatelet Strategy after Gastrointestinal Bleeding in Patients with Coronary Artery Disease?

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Abstract

Gastrointestinal bleeding after percutaneous coronary intervention (PCI) is a not too uncommon clinical situation and is associated with high morbidity and mortality. After initial treatment, a number of clinical decisions must be made weighing the risks of ischemic events and future bleeding. In particular, healthcare providers must carefully balance the effectiveness of antiplatelet therapy in the secondary prevention of coronary events, primarily future spontaneous myocardial infarction and stent thrombosis, against the risk of major, most commonly gastrointestinal bleeding. The first question is whether a dual antiplatelet therapy strategy is required or if a single antiplatelet agent will suffice. Then, if a single antiplatelet agent is adequate, which agent should be continued. Although there is some guidance to answer some of these questions, there are inadequate evidence-based data for others. Below, we review the various considerations and summarize our approach and rationale to manage patients who had gastrointestinal bleeding after PCI.

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Introduction

Clinical Vignette

A 63-year-old male with a past medical history of hypertension and coronary artery disease who underwent a percutaneous coronary intervention (PCI) of his first obtuse marginal branch of the circumflex coronary artery with a 2.5 mm × 15 mm second-generation everolimus-eluting stent 12 months ago for a non-ST segment elevation myocardial infarction (MI) presented to the emergency room with melena. The patient was hemodynamically stable, and physical exam was notable only for epigastric tenderness. His current medications included aspirin 81 mg daily, clopidogrel 75 mg daily, lisinopril 10 mg daily, metoprolol tartrate 25 mg twice daily, and atorvastatin 80 mg at night. Due to the concern for upper gastrointestinal (GI) bleeding, an upper GI endoscopy (EGD) was performed and showed an ulcer in the gastric body with stigmata of recent bleeding. Biopsies were taken from the gastric mucosa to evaluate for *Helicobacter pylori* and indicated no evidence of infection. The patient was diagnosed with aspirin-induced gastric ulcer and was started on a therapeutic course of a proton pump inhibitor (PPI). The patient presented to the cardiology clinic the following week seeking recommendations for antiplatelet therapy.

Table 1. Comparison of DAPT and PRECISE DAPT risk scores [17, 18]

DAPT		PRECISE DAPT
Age >75 years	−2	Age
Age 65 to <75 years	−1	Creatinine clearance
Age <65 years	0	Hemoglobin
Current cigarette smoker	1	White blood cell count
Diabetes mellitus	1	Previous spontaneous bleeding
MI at presentation	1	
Prior PCI or prior MI	1	
Stent diameter <3 mm	1	
Paclitaxel-eluting stent	1	
CHF or LVEF <30%	2	
Saphenous vein graft PCI	2	
Interpretation: a score of ≥ 2 is associated with a favorable benefit/risk ratio for prolonged DAPT while a score of <2 is associated with an unfavorable benefit/risk ratio		Interpretation: a sliding scale score is applied for each of the above variables, and the sum of their values is applied to a nomogram to approximate 1-year TIMI major bleeding and TIMI major or minor bleeding risk (see Fig. 2)
Validation: c-index for ischemia and bleeding of 0.70 and 0.68, respectively, in DAPT study patients, and 0.64 and 0.64, respectively, in the PROTECT trial validation cohort		Validation: c-index for out-of-hospital TIMI major or minor bleeding of 0.73 (95% CI: 0.61–0.85) in the derivation cohort, 0.70 (0.65–0.74) in the PLATO trial validation cohort, and 0.66 (0.61–0.71) in the BernPCI registry validation cohort
CHF, congestive heart failure; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.		

Duration of Dual Antiplatelet Therapy after Percutaneous Coronary Intervention

Numerous studies have compared various durations of dual antiplatelet therapy (DAPT) in patients after PCI [1]. Although many involved second-generation stents, these studies have spanned different generations of stents which further complicates recommendations for the optimal duration of DAPT after PCI. Based on 5 randomized controlled trials [2–6], 3–6 months of DAPT was found to be noninferior to 12 months of DAPT in low-risk patients (i.e., second-generation stents placed in patients with stable ischemic heart disease [SIHD]), in preventing stent thrombosis and ischemic events and had less GI bleeding, although these trials were individually underpowered to detect differences in stent thrombosis. On the other hand, in 6 randomized controlled trials [7–13] that used primarily second-generation drug-eluting stents, prolonged DAPT for up to 36 months beyond the initial 6- to 12-month treatment period was shown to reduce stent thrombosis and ischemic events at the expense of increased major nonfatal bleeding. Compared with a standard therapy of 6–12 months, an additional 18–36 months of DAPT after DES led to an absolute reduction in late stent thrombosis and ischemic complications (pri-

marily spontaneous MI) of 1–2% (RR 0.78, $p = 0.001$) at the tradeoff on an absolute increase of 1% in bleeding complications (RR 1.73, $p = 0.004$) [14]. Based on these studies and meta-analyses, the current class I guidelines for DAPT in patients who have undergone DES placement are a minimum of 6 months for those receiving PCI in the setting of SIHD and in those with PCI for ACS are a minimum of 12 months [1]. Recent trials regarding the use of ultra-short 1-month duration DAPT after single-vessel PCI for SIHD have shown noninferiority of DES to bare metal stents [15, 16]. Ultra-short-duration DAPT may be a consideration in some patients, but future studies directly comparing ultra-short DAPT duration to standard DAPT therapy are needed. Given the challenges in weighing the benefits and risks of prolonged DAPT, several investigators have developed risk scores to help the clinician weigh the risk/benefit ratio of ischemic events compared with bleeding, including the DAPT score [17] and PRECISE DAPT [18]. A high score indicates that the ischemic risk likely outweighs the risk of major bleeding. Factors that contribute to high-risk DAPT and PRECISE DAPT scores are shown in Table 1 and Figure 1. After completion of the minimum required DAPT, the physician should engage the patient in a process of shared decision-making and discuss the hazards

Fig. 1. Nomogram for bleeding risk calculation with PRECISE DAPT [18].

of bleeding and stent thrombosis/ischemic event risk and decide jointly if continuation of DAPT is of value.

In the case of the above patient who had a GI bleed 1 year after a newer generation DES for an ACS, the risk-benefit consideration would likely not favor continuation of DAPT and instead suggest continuation of antiplatelet monotherapy only. The patient does not have any increased risk factors for stent thrombosis or other ischemic risks and is at increased future bleeding risk due to his recent GI bleed. Here, the physician would need to consider which antiplatelet agent to resume, that is, aspirin or clopidogrel. There is no guidance in this regard, and below we review available information and considerations.

Mechanisms of Antiplatelet Therapy and Relevance to Gastrointestinal Injury

Aspirin

As first described by Vane [19] in 1971, aspirin blocks the production of prostaglandins. Cyclooxygenase is the rate-limiting step of prostaglandin and thromboxane synthesis, and aspirin nonspecifically and irreversibly inhibits cyclooxygenase by acetylating serine 516 [19, 20]. Aspirin inhibits the formation of thromboxane A_2 in platelets and inhibits autoactivation of surface thromboxane receptors which are required for the activation of glycoprotein 2b/3a (GP 2b/3a) [21]. Aspirin also induces nitrous oxide and modulates the transcription factor complex NF- κ B both of which play a role in reducing inflammation. Aspirin and other nonsteroidal anti-inflammatory drugs have both topical and systemic mechanisms that promote gastric or duodenal ulcer formation. Aspirin has a pKa of 3.50 and is not ionized in the acidic gastric lumen and can be absorbed across the pH-neutral gastric mucosa where it becomes ionized and trapped temporarily in gastric mucosal cells [22], causing local damage. Systemic inhibition of cyclooxygenase, including in the gastric mucosa, inhibits the conversion of arachidonic acid to prostaglandin G₂ which is later converted to prostaglandin H₂ and then to prostaglandin E₂. Prostaglandins increase local blood flow and increase synthesis and secretion of gastric mucus and bicarbonate. These topical and systemic effects, especially in combination with other factors that increase gastric acid secretion such as corticosteroid use, multiple NSAIDs, and age, ultimately result in a weakened mucosal barrier and a propensity for ulcer formation [23]. Once an ulcer has developed, the antiplatelet effects of aspirin increase the risk of bleeding. Efforts are underway to develop a safer aspirin

– a lipid-aspirin complex – that may reduce endoscopic GI ulceration compared with immediate-release aspirin and have better bioavailability and more consistent antiplatelet effects than enteric-coated aspirin [24, 25].

Clopidogrel

The formation of a stable platelet plug is dependent on the cross linking of pairs of platelet GP 2b/3a with fibrin. Clopidogrel is a thienopyridine antiplatelet agent which selectively and irreversibly inhibits ADP activation of the GP 2b/3a complex by forming a disulfide bridge at the ADP-binding site on the P2Y₁₂ G protein-coupled receptor [26]. Clopidogrel is a prodrug and is converted to its active metabolite in the liver through the cytochrome P450 system, including the 2C19 isoenzyme [27]. Clopidogrel has no topical effect on gastric mucosa, and this has been confirmed endoscopically. However, the antiplatelet effects of clopidogrel can predispose patients with gastric ulcers to bleeding, and there are some animal studies suggesting that clopidogrel delays gastric ulcer healing by inhibiting proangiogenic growth factors including vascular endothelial growth factor [28].

Therefore, just based on mechanism of action, it would seem that theoretically clopidogrel may be preferred in a patient who has experienced GI (especially upper) bleeding as aspirin not only increases bleeding when it occurs but is also ulcerogenic. While prasugrel and ticagrelor are also approved for the treatment of acute coronary syndrome, both have a higher incidence of major bleeding compared with clopidogrel (prasugrel 2.4% vs. clopidogrel 1.8%, p 0.03; ticagrelor 4.5% vs. clopidogrel 3.8%, p 0.03) [29, 30], and studies with monotherapy of these agents are just starting to emerge. Direct comparisons between aspirin and clopidogrel however exist and hence can provide some additional guidance in regard to which antiplatelet agent to use as monotherapy in the above-presented scenario.

Comparison of Aspirin and Clopidogrel for the Secondary Prevention of Cardiac Events

The largest head-to-head comparison of aspirin and clopidogrel was the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, an international randomized double-blinded trial of high-risk patients with recent ischemic stroke, MI, or symptomatic peripheral artery disease, comparing 9,546 patients assigned to aspirin 325 mg daily with 9,553 patients assigned to clopidogrel 75 mg daily. Clopidogrel was superior to

aspirin in reducing the primary endpoint of stroke, MI, or vascular death (absolute event rate of 5.83% for aspirin vs. 5.32% for clopidogrel, $p = 0.043$), while there was no significant difference in the mortality rate (3.11% vs. 3.05%; $p = 0.71$). There was a lower rate of hospitalization for ischemia or bleeding in the clopidogrel arm (12.4% vs. 13.6%; $p = 0.018$) [31]. Subgroup analyses showed that clopidogrel might be of greatest benefit for high-risk secondary-prevention patients, such as those with diabetes [32]. Although these results are statistically significant, the absolute difference in the trial overall is modest, and historically aspirin and clopidogrel have been considered to have similar efficacy and strength of recommendation in guidelines. Aspirin may in general have been preferred partially due to cost effectiveness; however, now that clopidogrel is generic, this may be less of a consideration.

Incidence of Primary Gastrointestinal Event in Patients on Antiplatelet Therapy

As previously discussed, aspirin increases the risk of peptic ulcer disease and GI bleeding by both topical and systemic mechanisms. Clopidogrel increases the risk of bleeding in a patient with an already established gastric ulcer and potentially impairs ulcer healing but does not have the same incidence of primary or recurrent ulcer formation after healing. The CAPRIE trial (1996) showed the incidence of any GI bleeding (2.66% vs. 1.99% $p < 0.05$) and severe upper GI bleeding (0.7% vs. 0.5% $p < 0.05$) was significantly higher in patients randomized to aspirin 325 mg compared with clopidogrel and led to a higher rate of medication cessation (0.93% vs. 0.52%; $p < 0.05$). 75–100 mg aspirin is currently the recommended and most commonly used dose in the setting of coronary artery disease. Small volunteer studies have shown that higher-dose (300–325 mg) aspirin is associated with increased mucosal damage compared with low-dose (75–100 mg) aspirin [33–36]. The ADAPTABLE Study is soon to be presented at ACC and may provide additional guidance on optimal dosing of aspirin.

Medical Therapy for Ulcer-Associated Gastrointestinal Bleed

After initial stabilization and management of an ulcer-associated bleed, patients should be tested and treated (when testing is positive) for *H. pylori* infections. Patients with a history of GI bleeding are at high risk for recurrent

bleeding. Prophylactic therapy with a gastroprotective agent is generally indicated, and PPIs have been shown in multiple studies and meta-analysis to be superior to other agents including H₂-receptor antagonists for the primary and secondary prevention of ulceration and bleeding [37–40]. As such, the American College of Gastroenterology guidelines currently recommend long-term PPI therapy for patients with a history of bleeding ulcers related to antiplatelet therapy [41]. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines also recommend the use of PPIs in patients on DAPT who have a history of GI bleeding (class I recommendation) and in patients at risk for GI bleed including those on oral anticoagulant therapy, female sex, advanced age, low body weight, chronic kidney disease, diabetes mellitus, anemia, and nonsteroidal anti-inflammatory medications (class IIa recommendation) [42–45].

Safety of Concomitant Antiplatelet and Gastroprotective Therapy with Proton Pump Inhibitors

There are conflicting data about the importance of the interaction between PPIs and antiplatelet agents. Cytochrome P450 2C19 plays a key role in the metabolism of both clopidogrel and PPIs, and competitive inhibition of this enzyme may decrease clopidogrel activation. Inhibition of clopidogrel activation may be clinically important since patients with less-active 2C19 alleles have impaired platelet inhibition on clopidogrel and may be at higher risk of cardiovascular events [46, 47]. Initial laboratory studies indeed demonstrated decreased platelet inhibition and lower serum clopidogrel metabolites when clopidogrel was given in combination with PPIs [48]. Gilard et al. [49] evaluated patients on aspirin and clopidogrel and found that omeprazole significantly decreased the platelet inhibitory effect of clopidogrel. Subsequent studies have suggested that decreased antiplatelet activity may not be a PPI class effect with studies showing that omeprazole and esomeprazole may be worse than other PPIs, but these results have not been consistent [50, 51]. Furthermore, even with omeprazole, taking clopidogrel and omeprazole 12 h apart may mitigate their interaction [52]. Most importantly, there is no clear evidence that these surrogate outcome markers are associated with adverse clinical outcomes [53]. Several large meta-analyses of retrospective and observational studies showed that patients on DAPT after PCI have higher major adverse cardiac events; however, there were no major adverse cardiovascular events

when pooling data only from randomized controlled trials [54, 55]. This dichotomy is likely the result of the increased medical complexity of patients who are prescribed PPIs [56]. The COGENT study which randomized 3,873 subjects on DAPT to omeprazole or placebo reported that the GI event rate including overt bleeding was significantly lower in the omeprazole arm, and the cardiac event rate was not different between the arms. Unfortunately, the study was terminated earlier than the planned 5,000 subjects due to sponsor losing funding [57]. The COMPASS trial was a 3×2 partial factorial, multicenter, double-blind, randomized placebo-controlled trial evaluating patients with stable atherosclerotic vascular disease. Participants were randomized to low-dose rivaroxaban with or without low-dose aspirin. All participants without a clinical indication for PPI (64%) were randomized to receive either pantoprazole 40 mg or placebo. There was no statistically significant difference in total upper GI events; however, there was a significant difference in overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography in those who received PPI therapy (0.2% vs. 0.4%; HR 0.52; p 0.03). The authors concluded that the routine use of PPIs in patients on low-dose anticoagulation and/or aspirin for stable cardiovascular disease did not reduce upper GI events but may reduce bleeding from gastroduodenal lesions [58].

As with clopidogrel, there is evidence for the interaction between aspirin and PPIs which may compromise the efficacy of aspirin [59–61]. After correcting for baseline risk imbalances and the differences, however, there is no significant difference in clinical outcomes [62]. Histamine (H_2) receptor antagonists also increase gastric pH but are not associated with increased cardiovascular risk [63]. Based on available evidence, there seems to be a mechanistic basis that would support that antiplatelet therapy efficacy may be affected by concomitant therapy with PPIs, but this has not translated to an increased risk for adverse cardiovascular outcomes in clinical studies. Given that clinical trials cannot inform the risk at an individual patient level, it would be prudent for the clinician to use concomitant PPI therapy only when clearly needed as suggested in the guidelines.

Comparison of Antiplatelet Therapies after GI Bleeding

There are small randomized studies suggesting mortality benefit of resuming low-dose aspirin after upper or lower GI bleeding [64, 65]. Several studies have sought to

compare aspirin with other antiplatelets for primary and secondary cardiac and cerebrovascular prevention in patients with GI bleeding; however, most of these studies have been small. Chan et al. [66] randomized 320 patients to 75 mg clopidogrel daily without PPI or aspirin 80 mg and esomeprazole 20 mg daily after an 8-week course of treatment for *H. pylori*-negative aspirin-induced peptic ulcer disease and found that patients assigned to clopidogrel had a higher bleeding rate; however, the study results are difficult to interpret given that patients in the clopidogrel arm were intentionally not given a PPI after randomization. A smaller study by Ng et al. [67] randomized 129 patients to clopidogrel with PPI or aspirin with PPI and found no difference in bleeding or treatment success rates. Hence, currently, there are only suboptimal data reporting on the comparison between antiplatelet strategies after GI bleeding.

Summary and Our Recommendations

The effectiveness of antiplatelet therapy for the secondary prevention of cardiovascular events has been very well documented. However, inherent to the mechanism of action, all of these antiplatelet agents increase the risk of bleeding. Addressing the choice of antiplatelet therapy for our patient with an aspirin-induced bleeding GI ulcer lies in balancing cardiovascular benefits with GI bleeding risks. Aspirin and clopidogrel appear to have similar efficacy for the prevention of coronary events with data perhaps suggesting that clopidogrel may have somewhat greater benefit in higher risk secondary prevention. Therefore, if from a cardiovascular standpoint there is equipoise, then the decision lies with preventing further or recurrent GI complications and addressing drug interactions. Mechanistically, aspirin would seem to have a higher risk of ulcer recurrence and bleeding due to topical effects and systemic prostaglandin inhibition. Head-to-head trial data in patients without a history of GI bleeding showed that aspirin has a higher primary GI bleeding rate compared with clopidogrel but used a higher dose of aspirin (325 mg) than what we would currently recommend (75–100 mg) for cardiovascular protection [30]. Even so, clopidogrel had greater efficacy than 325 mg aspirin in CAPRIE, and it would be reasonable to assume that it would have superior efficacy to 81 mg aspirin – however, this has not been studied. While the GI bleeding risk of 81 mg aspirin is lower than the higher-dose aspirin in the CAPRIE trial, clopidogrel likely remains a better choice with respect to the incidence of GI bleeding.

Fig. 2. Gastrointestinal (GI) bleed in a patient on antiplatelet therapy. *Recommend using risk scores DAPT and PRECISE DAPT for patient risk assessment.

The American College of Gastroenterology guidelines currently recommend long-term PPI therapy for all patients with a history of bleeding ulcers (not just for those on aspirin). The concern for PPI-clopidogrel and PPI-aspirin interaction from laboratory and observational studies has not been supported by randomized trials. Therefore, it is likely that the overall clinical significance of the interaction between various PPIs and antiplatelet agents is small, and longer-term randomized trials would be needed to determine if there is indeed a clinically relevant adverse drug-drug interaction.

Therefore, based on available clinical evidence including the mechanistic association between aspirin and GI ulcers, the likely superior efficacy of clopidogrel, and the lack of clear clinical implications from concomitant PPI use, we would recommend that patients with upper GI bleeding from an ulcer who need single antiplatelet therapy be treated preferentially with clopidogrel. It would be reasonable to use a PPI as well (Fig. 2).

Conflict of Interest Statement

Dr. Deepak L. Bhatt discloses the following relationships – Advisory Board: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, MyoKardia, Novo Nordisk, PhaseBio, PLx Pharma, and Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), and Population Health Research Institute; honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research

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