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Risk and management of upper gastrointestinal bleeding associated with prolonged dual-antiplatelet therapy after percutaneous coronary intervention

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Abstract Prolonged dual-antiplatelet therapy with aspirin and clopidogrel is mandatory after drug-eluting stent implantation because of the potential increased risk of late stent thrombosis. The concern regarding prolonged antiplatelet therapy is the increased risk of bleeding. Gastrointestinal bleeding is the most common site of bleeding and presents a serious threat to patients due to the competing risks of gastrointestinal hemorrhage and stent thrombosis. Currently, there are no guidelines and little evidence on how best to manage these patients who are at high risk of morbidity and mortality from both the bleeding itself and the consequences of achieving optimum hemostasis by interruption of antiplatelet therapy. Managing gastrointestinal bleeding in a patient who has undergone recent percutaneous coronary intervention requires balancing the risk of stent thrombosis against further catastrophic bleeding. Close combined management between gastroenterologist and cardiologist is advocated to optimize patient outcomes.

Keywords: Percutaneous coronary intervention; Drug-eluting stent; Gastrointestinal bleeding; Clopidogrel

1. Introduction

The use of dual-antiplatelet therapy (DAPT) with aspirin and a thienopyridine (clopidogrel or ticlopidine) in the setting of percutaneous coronary intervention (PCI) with stent implantation has become the standard of care to prevent stent thrombosis and recurrent ischemic events. Although rare, stent thrombosis is associated with high mortality and morbidity [1,2]. In the era of drug-eluting stents (DESs), prolonged antiplatelet therapy is mandatory because of the potential increased risk of late stent thrombosis secondary to delayed endothelialization associated with DES compared to bare-metal stents (BMSs) [3,4]. Current guidelines recommend DAPT for a minimum of 4 weeks after BMS and 12 months after DES implantation [5]. However, in clinical practice, duration longer than 12 months and even indefinite DAPT are often prescribed after DES implantation. The obvious concern with prolonged DAPT is an increase in bleeding risk. As PCI and DES are increasingly performed

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and used for the management of coronary artery disease, the prevalence of patients on prolonged DAPT is likely to increase. As a result, the incidence of bleeding complications as a consequence of DAPT is also likely to rise.

The upper gastrointestinal (UGI) tract is the most common site of GI bleeding and a potential target for preventative strategies. The literature regarding UGI bleeding after PCI for coronary artery disease is sparse. Until recently, little attention has been placed on the adverse impact of bleeding post-PCI. There are currently no guidelines in the management of bleeding post-PCI while on DAPT. This article aims to review the risk and management of UGI bleeding complications in patients on DAPT after PCI.

2. Evidence for prolonged DAPT after PCI

Patients with significant coronary artery disease are likely to have significant atherothrombotic burden and ongoing atherothrombosis elsewhere in the arterial system (cardiovascular, cerebrovascular and peripheral vascular). Therefore, longer courses of clopidogrel and aspirin after PCI may provide additional benefits.

In the PCI-Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, long-term clopidogrel after PCI with a mean of 8 months' follow-up was associated with a 17% relative risk reduction (P=.03) in combined cardiovascular death, myocardial infarction and revascularization [6]. The Clopidogrel for the Reduction of Events During Observation (CREDO) showed that 12 months of aspirin and clopidogrel provided a 27% reduction in relative risk of death, myocardial infarction or stroke in patients undergoing PCI compared with a 1-month regimen (P=.02) [7]. Experience with intracoronary radiation also showed that 12 months of DAPT was superior to a 6-month schedule, which was better than a 1-month regimen at reduction of adverse ischemic events [8]. The Duke study showed that 2-year mortality for patients treated with DES was lowest for those who remained on clopidogrel for at least 1 year and was highest in individuals not on this drug at 1 year [9]. Findings of other registry studies have also confirmed an increase in mortality and myocardial infarction with termination of clopidogrel 6–12 months after implantation of DES [10,11]. In conclusion, significant and robust evidence supports the recommendation of prolonged use of DAPT in high-risk coronary artery disease patients, particularly in DES population.

3. Duration of DAPT after DES implantation

The optimal duration of DAPT after DES implantation is not known. Previous recommendations for DAPT were for at least 3 months for the sirolimus-eluting stent and 6 months for paclitaxel-eluting stent but ideally for up to 12 months [12]. Currently, the U.S. Food and Drug Administration advisory committee has advocated 12 months of uninterrupted treatment, which is supported by the American Heart Association, the American College of Cardiology and the European Society for Cardiology [5]. A number of recent reports suggested that the risk of stent thrombosis and the associated adverse consequences of myocardial infarction and death are significantly increased after the cessation of clopidogrel therapy [10,11]. In a study by Spertus et al. [13], patients who stopped thienopyridine therapy by 30 days were more likely to die during the next 11 months [7.5% vs. 0.7%, P=.0001; adjusted hazard ratio (HR)=9.0, 95% confidence interval (CI)=1.3 to 60.6]. Given the high morbidity and mortality associated with these events, it may be preferable to continue DAPT indefinitely [3,11]. However, the optimum duration of DAPT must balance the benefit of reduced ischemic events against the harm from increased bleeding. Whether a longer regimen would provide additional benefit with acceptable bleeding risk is unknown. Only a prospective randomized clinical trial can properly address this question.

4. Risk of GI bleeding and antiplatelet therapy

4.1. Aspirin monotherapy

Aspirin leads to suppression of mucosal prostaglandin synthesis and subsequent formation of mucosal erosions. Whereas the inhibition of thromboxane-A2-mediated platelet function is dose independent (at least for daily doses >30 mg), the impairment of PGE2-mediated cytoprotection in the GI mucosa is dose dependent [14]. Aspirin amplifies the risk of bleeding by causing new mucosal lesions or aggravating existing ones, which are associated with a greater relative risk (four- to sixfold) at the higher doses of aspirin [14]. Of patients with a history of peptic ulcer bleeding who continue to take aspirin after ulcer healing and eradication of *Helicobacter pylori* infection, up to 15% experience recurrent bleeding within a year [15].

4.2. Clopidogrel monotherapy

Whether clopidogrel causes mucosal injury and bleeding from preexisting mucosal lesions is uncertain. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial, GI hemorrhage (0.52% vs. 0.72%, P< .05) was significantly less frequent with clopidogrel compared with aspirin [16]. Available evidence suggests that clopidogrel does not induce new ulcer formation but may cause rebleeding due to impaired hemostasis only in subjects with underlying mucosal defects or scarring [17]. In randomized controlled trials, among patients with acute coronary syndrome (ACS), the addition of clopidogrel to aspirin appears to increase the relative risk of all hemorrhagic events by 50% [18]. However, it must be remembered that the patients in these trials also received other antithrombotic medication including glycoprotein IIb/IIIa inhibitors and

heparin; moreover, the definition of major bleeding varied between trials, making comparison less than straightforward.

4.3. Dual-antiplatelet therapy

The increasing use of DAPT puts more patients at risk from GI injury and bleeding. The risk of GI bleeding is significant (1.3%) within 30 days of combined antiplatelet therapy and as high as 12% in a high-risk population with prior peptic ulcer bleeding [17,19]. The risk of adverse GI events depends on the dose and duration of antiplatelet therapy. In the CURE study, the risk of GI bleeding up to 1 year with combination clopidogrel (75 mg) with high-dose aspirin (>200 mg) is significantly greater than that with low-dose aspirin (≤100 mg) (3% vs. 4.9%, *P*=.0009) [20].

In the CREDO trial, long-term clopidogrel plus aspirin therapy was associated with a nonsignificant trend toward an increase in major bleeding of 8.8% versus 6.7% (*P*=.07) in the monotherapy group at 1 year [7]. Data on the incidence of GI bleeding episodes were not provided, but approximately two thirds of all major bleeds occurred in patients undergoing coronary artery bypass graft surgery.

Most of the bleeding risk with DAPT appears to occur fairly early after initiation of treatment. Data from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance (CHARISMA) trial noted similar rates of moderate-to-severe bleeding after DAPT compared with aspirin alone after 270 days [21]. Thus, a patient who has tolerated dual regimen for 9–12 months, without occurrence of any bleeding episodes that led to discontinuing the antiplatelet regimen, may be safe to continue DAPT beyond 12 months. The CHARISMA analysis suggests that such individuals are unlikely to have an appreciable incremental bleeding risk with an extended duration of DAPT compared with the baseline risk with aspirin alone [21].

In patients requiring warfarin therapy, the addition of DAPT is associated with an approximately three- to sixfold increase in bleeding events [22].

4.4. Novel antiplatelet agents

Prasugrel is a third-generation oral thienopyridine that has more potent antiplatelet activity, faster onset of action and less interpatient variability in response compared with clopidogrel. These pharmacodynamic properties lead prasugrel to be more efficacious in preventing ischemic events and an increased risk of bleeding. In the TRITON-TIMI 38 trial, TIMI major bleeding was observed in 2.4% of patients receiving prasugrel and 1.8% of patients receiving clopidogrel (HR=1.32, 95% CI=1.03–1.68, *P*=.03) in 13,608 patients with moderate- to high-risk ACS who were undergoing PCI [23]. The rate of life-threatening bleeding was greater in the prasugrel group than in the clopidogrel group (1.4% vs. 0.9%, *P*=.01), which included nonfatal bleeding (1.1% vs. 0.9%, *P*=.23) and fatal bleeding (0.4% vs. 0.1%, *P*=.002). In general, both TIMI major and minor bleeding episodes were more frequent with prasugrel than with clopidogrel.

Three other novel non-thienopyridine antiplatelet agents — cangrelor, ticagrelor and SCH 530348 — are in advanced clinical testing in patients with coronary artery disease. Cangrelor and ticagrelor are direct and reversible inhibitors of the platelet P2Y12 receptor, whereas SCH 530348 is a thrombin receptor antagonist. Clinical data available to date for each of these compounds suggest that they have safety and efficacy profiles that will be advantageous to patients with ACS undergoing PCI [24].

5. Consequence of bleeding post-PCI

In the past, bleeding and blood transfusions were considered problematic but not potentially life threatening. More recently, the association between bleeding and worse prognosis has been proven in patients with ACS and undergoing PCI with a stepwise increase in short- and long-term mortality with increasing bleeding severity [25,26]. In the OASIS and CURE studies, there was a close relationship between major bleeding and subsequent myocardial infarction, stroke and death at 30 days; that is, approximately 10% of patients who received two or more units of blood transfusion died within 30 days compared with 2.5% of those who did not sustain a bleed [25]. This finding is not surprising, because patients who present with hemorrhagic complications are frequently older, with significant comorbidities such as renal insufficiency. Therefore, bleeding may be a marker of a sicker patient, which confers an increased risk of death; the presence of major bleeding related with PCI appears to be an independent predictor of adverse outcomes in many registries [25,26]. However, there are no specific data published from ACS trials on the prognostic impact of GI hemorrhage.

It is necessary to understand the immediate mechanisms by which hemorrhage may affect post-PCI patients and increase their risk of major cardiac events. First, if hemorrhage is significant, it can produce intravascular volume depletion, tachycardia and an increase in myocardial demand, decreased perfusion and recurrent ischemia. Second, the treatment of significant bleeding frequently includes the interruption of antithrombotic therapy and blood transfusion. These interventions may be necessary but pose a very substantial risk of recurrent ischemia and stent thrombosis. This is particularly important in the current era of DES. Finally, transfusion therapy can potentially trigger inflammatory mediators that can theoretically increase the risk of stent thrombosis [27]. Studies examining blood transfusion in patients with coronary heart disease have yielded conflicting results, but several studies point to harmful effects [28–30]. Blood transfusions for patients with low hematocrit even without overt bleeding were associated with a higher risk of morbidity and mortality [28]. All of these interrelated events

ultimately can lead to myocardial infarction. Therefore, the discontinuance of DAPT and the initiation of blood transfusion as part of the treatment of post-PCI hemorrhage need to be thoroughly analyzed on an individual basis.

6. Preventive strategies

6.1. BMS or balloon angioplasty alone

Patients should be assessed for bleeding abnormalities before stent implantation, which could pose a contra-indication to use of a DES (Table 1). Known bleeding disorders that would favor use of a BMS or balloon angioplasty alone include a history of severe GI bleeding or any hereditary or acquired bleeding abnormality. Individuals with atrial fibrillation, a mechanical heart valve or a hypercoagulable state that needs lifelong anticoagulation with warfarin already have enhanced baseline risk for bleeding [31]. In such patients, the bleeding risk from additional long-term DAPT would also tend to favor use of a BMS or balloon angioplasty alone.

6.2. Prophylactic proton pump inhibitor and H. pylori eradication

The routine use of proton pump inhibitors (PPIs) or cytoprotective agents is not recommended in patients taking daily doses of aspirin in the range of 75–100 mg since no randomized trial has demonstrated the efficacy of such a GI-protective strategy in this setting [14]. On the other hand, patients who had ulcer complications related to the long-term use of low-dose aspirin and treatment with a PPI, in addition to the eradication of *H. pylori* infection, significantly reduced the rate of recurrence of ulcer complications: 1.6% in the lansoprazole (30 mg/day) plus aspirin (100 mg/day) group compared with 14.8% in the placebo plus aspirin group after 1 year of treatment (P=.008) [15]. In another study, the use of a PPI was associated with an 80% decrease in the risk of UGI bleeding in subjects taking low-dose aspirin [32]. Therefore, a useful option for patients who have experienced an ulcer complication while on aspirin and who need to continue their antiplatelet therapy is to take aspirin together with a PPI after eradication of any coexistent *H. pylori* infection and ulcer healing. However, the ulcerogenic effect of aspirin is not completely abolished by the eradication of *H. pylori* infection [15]. In another study, patients with aspirin-induced peptic ulcer disease treated with omeprazole (20 mg/day) randomized to receive clopidogrel or to continue with low-dose aspirin presented similar clinical and endoscopic outcomes after 8 weeks' follow-up [33].

Prolonged acid-suppression therapy with PPI may be reasonable for patients requiring prolonged DAPT after DES implantation. Unfortunately, there are no data available from the randomized clinical trial. The ongoing randomized COGENT-1 (Clopidogrel and the Optimization of Gastro-intestinal Events; NCT00557921) trial should provide evidence to help address the place of omeprazole after PCI in patients who required DAPT longer than 1 year. The available evidence in studies with patients on dual therapy is conflicting and scant. A recent study evaluating UGI bleeding risk in patients on aspirin and clopidogrel found that after adjustment for age, dose of aspirin, previous UGI bleeding and duration of treatment, the risk was marginally reduced by histamine-2 receptor antagonists (OR=0.43, 95% CI=0.18–0.91, P=.04) and significantly reduced by PPI (OR=0.04, 95% CI=0.002–0.21, P=.002), as compared to control [34]. In this study, the occurrence of UGI bleeding associated with DAPT was 4.0% [34]. Another study, however, found that there was no significant difference in the incidence of UGI bleeding between patients receiving and those not receiving PPI (0.7% vs. 0.6%, P=.88) [35]. Current practice suggests that where aspirin and clopidogrel are to be started or continued in patients with a recent history of UGI ulceration or bleeding (after ulcer healing and eradication of *H. pylori* infection), treatment with a PPI is a useful precaution. However, clinical trials are needed to support this strategy.

Table 1
Relative contraindication to DESs that would favor use of BMSs

1. Adherence to prolonged DAPT?
Polysubstance abuse
Dementia
Limited financial means
2. Bleeding risk?
a. Known bleeding disorder
Gastric ulcer
Esophageal varices
Diverticulosis
b. Potential bleeding disorder (lifelong warfarin)
Mechanical heart valve
Atrial fibrillation
Prothrombotic disorder
3. Surgery within the next year?
Many procedures require termination of antiplatelet

6.3. Low-dose antiplatelet therapy

The risk of UGI bleeding associated with medium-to-high doses of aspirin can be reduced to a relative risk of twofold versus nonusers by using the lowest effective dose of the drug (i.e., 75–160 mg/day). In the CURE study, the risk of GI bleeding up to 1 year with combination clopidogrel (75 mg) with high-dose aspirin (>200 mg) is significantly greater than that with low-dose aspirin (≤100 mg) (3% vs. 4.9%, P=.0009) [20]. The risk of GI bleeding associated with aspirin use cannot be further reduced by enteric-coated or buffered formulations.

7. Management of bleeding on DAPT

In the absence of specific guidelines for the management of UGI hemorrhage in patients on DAPT and the paucity of

published data on current practices in this cohort, the current recommended practice is based on treatment for UGI bleeding in general. ACS patients with low-risk GI lesions should probably have minimal interruption of antiplatelet therapy and can often be managed conservatively with respect to blood transfusion. Judicious transfusion should be given for hemodynamically significant blood loss. After or during rectification of the anemia, the aim is to determine the source of bleeding and to treat it appropriately. In the majority of cases, the site of bleeding is in the UGI tract and arterial in origin [19,36]. Early endoscopy is recommended for risk stratification and therapeutic interventions [37,38]. The risk of stent thrombosis associated with interruption of antiplatelet therapy needs to be balanced against the risk of continuing bleeding (Fig. 1).

7.1. Blood transfusion

In 1992, the American College of Physicians proposed guidelines for blood transfusion [39]. According to those guidelines, the decision to administer a blood transfusion to a patient should not be based on a hemoglobin trigger but rather on a patient's symptoms and on the risk of ischemic complications from acute anemia. In the setting of acute anemia secondary to blood loss, crystalloid infusions should be tried first, and single units should be transfused rather than what has been anecdotally the standard of 2 units of packed red blood cells. In addition, the decision to proceed with blood transfusion should be based on the presence of symptoms defined as transient ischemic attack, syncope, chest pain and sinus tachycardia as well as on the patient's risk of ischemic complications from the acute blood loss. A patient's risk is defined as the presence of unrevascularized coronary artery territory, valvular heart disease and congestive heart failure. According to the guidelines, in the absence of risk factors and of symptoms, patients should not be given a blood transfusion regardless of their hemoglobin level. However, few studies have attempted to validate appropriateness of blood transfusion according to these criteria.

There is evidence that preexisting anemia is associated with adverse outcomes in patients with acute myocardial infarction undergoing PCI [40]. However, correction of anemia may not improve prognosis and indeed may be hazardous. In the CRUSADE National Quality Improvement Initiative, patients who received transfusion appeared to confer an adverse outcome even after adjustment for other identifiable clinical factors [29]. In a prospective randomized trial comparing a liberal transfusion strategy (target hemoglobin between 10.0 and 12.0 g/dl) with a restrictive strategy (target hemoglobin between 7.0 and 9.0 g/dl) among patients with a wide range of illnesses, a higher threshold for transfusion was associated with lower in-hospital mortality [30]. Subgroup analysis revealed conflicting messages such

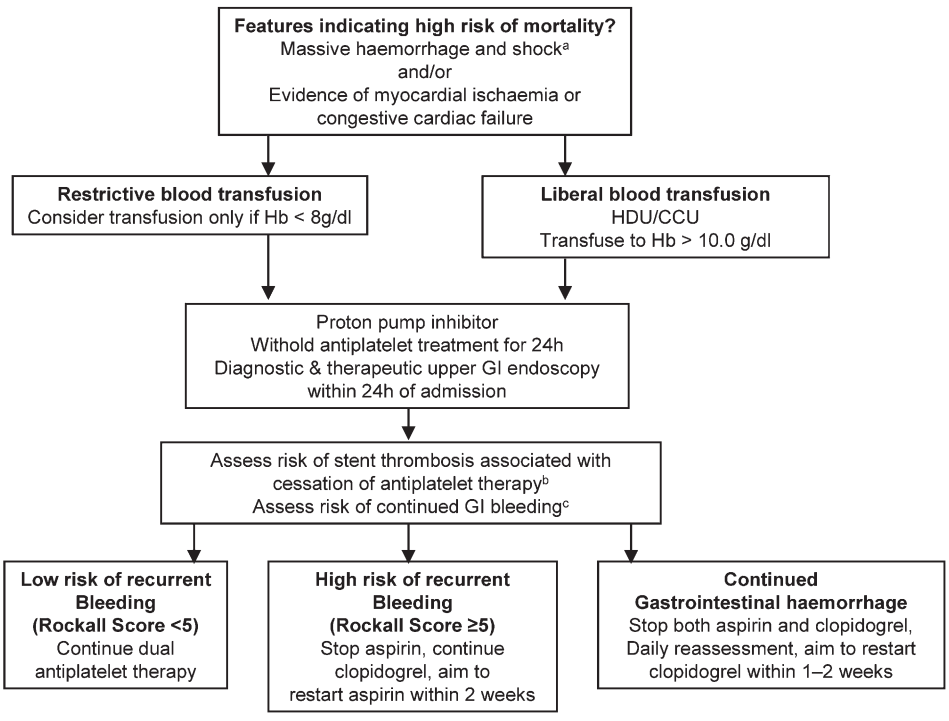

Fig. 1. Suggested management of UGI bleed after recent stent implantation. CCU, coronary care unit; HDU, high dependency unit. [a]SBP<100 mmHg, HR>100 bpm. Clinical assessment may be complicated by the impact of cardiac medication on blood pressure and pulse. [b]Factors associated with a high risk of stent thrombosis: impaired LV systolic function, diabetes mellitus, renal failure, long segment of stent (>20 mm) and recent coronary intervention (within 3 months of BMS, within 12 months of DES). [c]Factors associated with increased risk of continued bleeding: endoscopic diagnosis (visible vessel and stigmata of recent hemorrhage).

as significantly increased rates of myocardial infarction and pulmonary edema in the liberally transfused group but a nonsignificant trend toward adverse outcome in the subgroup of patients with preexisting coronary disease who received a restrictive transfusion policy. These apparently disparate findings may be explained by differences in physiological adaptation and the strain already present on cardiac reserve in response to preexisting anemia. Thus, in patients with chronic anemia, transfusion needs may differ from those in patients who become anemic as a result of acute blood loss in the context of ACS. Transfusion requirements have to be individualized for these complex patients. It is unlikely that a single transfusion threshold will be suitable for all. A restrictive transfusion policy would be appropriate, maintaining the hemoglobin above 8 g/dl. Ongoing evidence of ischemia or cardiac failure would merit a higher hemoglobin target.

7.2. Interruption of antiplatelet therapy

The potential risk of interrupting antiplatelet therapy is influenced by the presence of risk factors for stent thrombosis, the location of the stent and the amount of viable myocardium subtended by the stented vessel. Stent occlusion in a proximal vessel subtending viable myocardium may be fatal, whereas occlusion of a stent in a marginal branch subtending infarcted territory may pass unnoticed. Cessation of aspirin prescribed for primary or secondary prevention was associated with a 1.8-fold relative risk of arterial thrombosis in a meta-analysis of studies involving more than 50,000 patients with coronary artery disease [41]. The risk is greater for patients who have had an ACS. Premature discontinuation of antiplatelet therapy is the most important predictor of early stent thrombosis. A prospective observational analysis of 2229 consecutive patients receiving DES reported stent thrombosis in 1.3% of cases within 9 months [3]. In this study, premature antiplatelet therapy discontinuation (HR=89.78, 95% CI=29.90–269.60, $P<.001$) was the strongest independent predictor of stent thrombosis [3]. There is evidence of a rebound thrombotic effect following cessation of clopidogrel in the context of DAPT [42].

Measures of platelet function such as aggregation and bleeding time remain altered for up to 5 days after stopping clopidogrel or aspirin in healthy volunteers [43]. The period for which therapeutic antithrombotic effect remains is unknown and may be shorter in patients who are actively bleeding. In the event of a significant UGI hemorrhage, aspirin and clopidogrel can be safely withheld for 24 h. An assessment of the risk of sustained bleeding during this period can be made and will depend heavily on the findings at diagnostic endoscopy. Ultimately, the decision to restart antiplatelet therapy must balance the perceived risk and likely consequence of stent thrombosis against the possibility of continuing or recurrent hemorrhage. It is obviously important to establish the details of any coronary procedures the patient has undergone before making this judgment.

Clopidogrel is more effective than aspirin as monotherapy for the prevention of coronary thrombosis despite increased bleeding during surgery [44]. On the other hand, aspirin is more likely to have a causative role in UGI injury, and withholding aspirin may facilitate mucosal healing. For these reasons, and in the absence of trial evidence that might support a clinical guideline, clopidogrel should be recommenced within 1 or 2 days and aspirin should be recommenced within 1–2 weeks (depending on the degree of gastrointestinal injury), after a significant GI bleed.

7.3. UGI endoscopy

The frequency of early endoscopy and multimodality endotherapy is increasing in the management of UGI hemorrhage. Endoscopy with visualizing of the bleeding source helps risk stratification and allows therapeutic intervention. Although trials have not consistently demonstrated an impact on mortality, there is a strong consensus among gastroenterologists that early endoscopy reduces the risk of rebleeding, the need for surgical intervention and blood transfusion requirements [37,38]. Current guidelines for endoscopy in any patient presenting with UGI hemorrhage emphasize the importance of prior resuscitation. The major risk from this procedure is cardiorespiratory depression associated with sedation. Early endoscopy (within 24 h) is recommended for significant UGI hemorrhage, assuming no evidence of ongoing myocardial ischemia or any significant desaturation related to congestive cardiac failure.

A study of more than 4000 patients presenting with acute UGI hemorrhage identified independent variables predictive of mortality [45]. These included age, presence of shock, comorbidity and information obtained from endoscopy including the underlying diagnosis and whether there was direct evidence of active or recent bleeding (stigmata of recent hemorrhage). The investigators devised a scoring system (the Rockall score) based on five variables (Table 2) that predicted mortality and rebleeding [45]. Patients with cardiac or renal failure had among the highest rates of mortality. Patients with varices or peptic ulceration had an adverse outcome, particularly if active bleeding, a visible vessel or adherent clot was present. By contrast, patients with erosions or esophagitis followed a relatively benign course. The findings at diagnostic endoscopy are, therefore, very valuable in risk stratification. The risk factors for repeat or continued bleeding are similar to those for mortality, and rebleeding is in itself a potent predictor of mortality in all groups. There is good correlation between Rockall score, rebleeding and mortality [45].

Although patients with myocardial infarction are perceived to be at higher risk of complications, this is not the case for hemodynamically stable patients. A case–control study of 200 patients who underwent gastroscopy within 30 days of a myocardial infarction found that the complication rate was 7.5% compared with 1.5% in the controls [46]. The complications were largely confined to hemodynamically

Table 2
Rockall scoring system for risk of rebleeding and death after admission to hospital with acute gastrointestinal bleeding

Score	0	1	2	3
Age (years)	<60	60–79	>80	
Shock	No shock Systolic BP>100 mmHg HR<100 bpm	Tachycardia HR>100 bpm Systolic BP>100 mmHg	Hypotension Systolic BP<100 mmHg HR>100 bpm	
Comorbidity	Nil major		Cardiac failure Ischemic heart disease	Renal failure Liver failure Disseminated malignancy
Endoscopic finding	No lesion Mallory–Weiss tear with no SRH	All other diagnosis	Malignancy of UGI tract Adherent clot Visible or spurting vessel	
Major SRH	None or dark spot			

SRH, stigmata of recent hemorrhage.

unstable patients and most were cardiorespiratory, in particular hypotensive episodes (5.5%).

There is limited comparative evidence to choose between endotherapeutic techniques. Where there is active bleeding or a visible vessel, common practice would be dual therapy with a combination of large-volume (10–20 ml) epinephrine injection (1:10,000) and either thermal therapy with a heater probe or mechanical treatment with clips. While submucosal injection of epinephrine into ulcers can be detected in the circulation, there were no case reports of associated arrhythmias [47].

In patients with history of peptic disease or bleeding from an acid-related lesion, PPI and *H. pylori* eradication reduce the risk of rebleeding even when antiplatelet therapy is continued. Unfortunately, despite therapeutic endoscopy, high-risk endoscopic lesions have a 10–20% chance of further bleeding [48].

7.4. Lower GI endoscopy

Colonoscopy may be undertaken at slightly higher risk in patients with recent myocardial infarction. In a case–control study of 100 patients who underwent the procedure within 30 days of myocardial infarction, there were no serious complications related to the procedure [49]. Barium enema is probably lower risk, and computed tomography or MR virtual colonoscopy is now widely available. Antiplatelet agents may not substantially increase the risk of bleeding during therapeutic colonoscopy [50].

7.5. Need for urgent surgery

There is currently no guideline on how to manage patients who have already received a DES and need an urgent or elective surgical procedure. Some degree of antiplatelet treatment should be continued perioperatively if the surgical procedure allows. In coronary artery bypass grafting, perioperative use of aspirin is not only safe but also associated with enhanced survival [51]. Since risk for thrombosis is so high with premature termination of antiplatelet treatment (<6 months after DES implantation), use of an in-hospital bridge — consisting of a glycoprotein IIb/IIIa inhibitor, heparin (or low-molecular-weight heparin) or both — might be considered for patients at very high risk, such as those with a recent unprotected left main bifurcation stent. If this type of regimen is used, a short-acting glycoprotein IIb/IIIa inhibitor such as eptifibatide or tirofiban could be considered [52,53]. Such an approach needs to be further assessed prospectively with a randomized clinical trial. In the future, intravenous adenosine diphosphate receptor antagonists may have therapeutic merit.

8. Conclusion

The increasing use of prolonged DAPT after PCI and DES implantation puts more patients at risk from gastrointestinal injury and bleeding. Bleeding after coronary intervention is a major issue for patients on dual-antiplatelet agents. Most gastrointestinal hemorrhage occurs in the UGI tract. Preventive strategies include avoiding implantation of DESs in patients deemed at high risk of bleeding, prophylactic PPI and *H. pylori* eradication. The current state-of-the-art management of significant UGI bleed includes blood transfusion, treatment targeting the site of bleeding including early endoscopy and reconsideration of

Table 3
Recommendations for UGI bleeding associated with DAPT

Preventive strategies
Balloon angioplasty alone or BMSs for patients at high risk of bleeding or contraindication to prolonged DAPT
Prophylactic PPI and *H. pylori* eradication
Low-dose aspirin therapy (75–160 mg)
Management of bleeding on DAPT
Judicious blood transfusion for hemodynamically significant blood loss
Balance risk of stent thrombosis against risk of ongoing bleeding with minimal interruption of antiplatelet therapy
Early endoscopy for risk stratification and therapeutic interventions
PPI and *H. pylori* eradication
Consider bridging antiplatelet therapy for patients in need of urgent surgery

the need for continuation of DAPT (Table 3). However, more work is required in this area. Antiplatelet treatment should always be viewed as a balance between antithrombotic effect and risk of excessive bleeding. The consequences of bleeding include a high risk of death and myocardial infarction and the need for transfusion, which is potentially deleterious. Prevention of bleeding has become as equally as important as the prevention of ischemic events.

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