

Treatment and prevention of gastrointestinal bleeding in patients receiving antiplatelet therapy

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antiplatelet therapy with proton-pump inhibitors (PPIs) is recommended to prevent further ischemic events. PPI prophylaxis during antiplatelet therapy reduces the risk of upper gastrointestinal bleeding. The potential negative metabolic interaction between PPIs and clopidogrel is still unclear.

Key words: Antiplatelet therapy; Aspirin; Clopidogrel; Gastrointestinal bleeding; Endoscopy; Proton-pump inhibitor

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Core tip: Gastrointestinal bleeding (GIB) is a relatively common complication in patients receiving antiplatelet therapy and is associated with an increased risk of recurrent ischemic events and mortality. Early endoscopy is useful for both the diagnosis and the therapeutic management of GIB. Antiplatelet therapy should be resumed immediately after endoscopic hemostasis of GIB, unless the bleeding is life threatening. Prophylaxis with antisecretory drugs such as proton-pump inhibitors reduces the risk of GIB.

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Abstract

Antiplatelet therapy is the standard of care for the secondary prevention of acute coronary syndrome and ischemic stroke, especially after coronary intervention. However, this therapy is associated with bleeding complications such as gastrointestinal bleeding, which is one of the most common life-threatening complications. Early endoscopy is recommended for most patients with acute upper gastrointestinal bleeding. After successful endoscopic hemostasis, immediate resumption of

INTRODUCTION

Antiplatelet therapy is widely used in the secondary prevention of acute coronary syndrome (ACS) and ischemic stroke, especially after interventional

therapy. Dual antiplatelet therapy (DAPT) with aspirin plus a thienopyridine derivative that inhibits the platelet P2Y₁₂ adenosine diphosphate (ADP) receptor is the standard treatment to prevent stent thrombosis after implantation of drug-eluting stents (DESs) in patients with symptomatic coronary artery disease^[1,2]. The joint guidelines of the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions recommend that aspirin therapy should be continued lifelong in all patients with ST-elevation myocardial infarction (MI)-ACS, and clopidogrel or prasugrel should be administered for at least 12 mo in patients receiving stents (bare metal stents or DESs) during percutaneous coronary intervention (PCI) for ACS^[3,4]. Antiplatelet therapy is also used for both the management and the prevention of acute ischemic stroke. Aspirin is the most commonly used agent in this therapy. Long-term administration of clopidogrel in patients with ischemic stroke is also beneficial and induces a slightly lower frequency of gastrointestinal bleeding (GIB) than does aspirin administration^[5].

Antiplatelet therapy is associated with bleeding complications such as GIB, which is one of the most common life-threatening complications of this therapy^[6-9]. This review focuses on the management and prevention of upper GIB in patients receiving antiplatelet therapy.

ANTIPLATELET THERAPY AND GIB

Antiplatelet therapy causes GIB, especially in elderly patients. Usually, clinically important upper GIB is identified by hematemesis and/or melena and a decrease in hemoglobin level of at least 2 g/dL, and is confirmed by an endoscopic diagnosis of peptic ulcer lesions as the cause of bleeding. Antiplatelet therapy-related ulcers often occur without symptoms of dyspepsia. Aspirin and P2Y₁₂ inhibitors are the most common antiplatelet agents. Aspirin irreversibly inhibits cyclooxygenase-1 by acetylating a serine residue at position 530, thereby preventing the conversion of arachidonate to the prostaglandin PGH₂, which is converted to the platelet agonist thromboxane^[10]. Several randomized trials (RCTs) have documented that patients with prior cardiovascular disease experience fewer cardiovascular events and deaths with the use of low-dose aspirin (LDA) therapy than without its use^[11,12]. LDA is commonly defined as aspirin between 75 and 325 mg/d. A meta-analysis indicated that no additional benefit was observed with the use of a higher dose of aspirin (300 mg/d vs 50-100 mg/d^[12]). LDA is an effective therapy for the secondary prevention of cardiovascular events and ischemic stroke.

Thienopyridines affect the ADP pathway by irreversibly blocking the ADP receptor P2Y₁₂, thereby inhibiting the activation of the glycoprotein II b/III

a complex and platelet aggregation^[10,13]. Ticlopidine, clopidogrel, and prasugrel are thienopyridine prodrugs that require conversion to an active metabolite. Ticagrelor belongs to a new family of antiplatelet agents, which directly and reversibly bind to the P2Y₁₂ receptor. The antiplatelet effects of the P2Y₁₂ inhibitor are additive to those of aspirin. The benefits of DAPT over aspirin alone in patients with ACS without ST-segment elevation were established in the Clopidogrel in Unstable Angina to Prevent Recurrent Events CURE trial^[14]. Analysis of a subset of patients in the CURE trial also showed the efficacy of DAPT in PCI^[15].

Incidence and risk factors of GIB

The reported risk factors for upper GIB include increasing age, female sex, major organ dysfunction (cardiac, respiratory, or hepatic), diabetes, hypertension, positive results for *Helicobacter pylori* infection, and hemostatic disorders^[7,16,17]. A case-control study showed that the odds ratios (ORs) for upper GIB in patients receiving LDA were similar to those in patients regularly receiving nonsteroidal anti-inflammatory drugs^[18]. A meta-analysis showed that there was an increased risk of major GIB with LDA use (OR = 1.55; 95%CI: 1.27-1.90^[19]). The risk of upper GIB associated with the use of thienopyridine monotherapy is reported to be similar to^[17] or greater than that associated with the use of aspirin alone^[14]. The risk of major bleeding is reportedly increased in patients receiving DAPT compared with those receiving aspirin monotherapy^[20]. In a population-based observational cohort study of elderly patients who survived MI, the rate of GIB was 1.5% per year with aspirin alone and 4.6% per year with aspirin plus clopidogrel or ticlopidine^[21]. Several large RCTs^[14,22-25] reported that 0.6% (28-d follow-up) to 4.8% (12-mo follow-up) of patients treated with DAPT experienced major bleeding, as compared with 0.6% (28-d follow-up) to 3.8% (12-mo follow-up) of patients treated with aspirin alone. An observational study reported that the 1- and 2-year cumulative incidences of upper GIB in patients who received DAPT without the use of an antisecretory drug [proton-pump inhibitor (PPI) or histamine-2 receptor antagonist (H2RA)] were 4.5% and 9.2%, respectively^[9]. Of note, the first month after PCI is a high-risk period for upper GIB^[9,17,26]. Further, the risk of GIB with triple therapy with warfarin, aspirin, and clopidogrel was reported to be as high as 5.1%^[27].

Outcomes of GIB

Bleeding complications are associated with an increased risk of recurrent ischemic events and death^[26,28]. In particular, GIB complicating PCI is associated with early mortality. In the Acute Catheterization and Urgent Intervention Triage Strategy trial, a large multicenter trial in patients



Figure 1 Peptic ulcer with an exposed vessel in a 68-year-old man 10 d after starting dual antiplatelet therapy after percutaneous coronary intervention for acute myocardial infarction.



Figure 2 Successful endoscopic hemostasis using endoclips.

with moderate- and high-risk ACS, GIB occurred in 1.3% of the patients and was found to be associated with longer hospital stays and higher 30-d all-cause mortality rates (9.6% vs 1.4% in patients with no bleeding^[29]). A retrospective study reported that the 30-d mortality rates were as high as 20.5% in patients with GIB, compared to 2.4% in those without GIB^[30]. The mechanism underlying the high rates of early mortality in ACS patients with GIB may be multifactorial. The risk of ischemic events is further aggravated by the augmented release of endogenous catecholamines and increased platelet adhesiveness in ACS patients with bleeding complications. Importantly, GIB is a well-known cause of premature cessation of antiplatelet therapy, which poses a serious risk of ischemic events during hospital stay and after hospital discharge.

MANAGEMENT OF GIB IN PATIENTS RECEIVING ANTIPLATELET THERAPY

Impact of blood transfusion on mortality after PCI

Major GIB often requires red blood cell (RBC) transfusions. Although RBC transfusions are performed to augment oxygen delivery to avoid the deleterious effects of oxygen debt, these transfusions may have potential harmful effects^[31]. Indeed, despite increased hemoglobin levels, RBC transfusion does not always increase tissue oxygenation. One possible explanation is that stored RBCs are low in 2,3-diphosphoglyceric acid; therefore, the hemoglobin will tend not to release oxygen to the tissues. In addition, RBCs mediate a nitric oxide-based hypoxic vasodilatory activity, which is impaired in banked blood, predisposing to vasoconstriction and ischemic insult^[32]. Therefore, blood transfusion does not always provide beneficial effects in ACS patients^[33]. A recent RCT in patients with acute upper GIB showed that a restrictive transfusion strategy (*i.e.*, transfusion when the hemoglobin level was < 7 g/dL) had significantly better outcomes than

a liberal transfusion strategy (*i.e.*, transfusion when the hemoglobin level was < 9 g/dL^[34]). Therefore, in patients with stable hemodynamic status, RBC transfusion is considered when the hemoglobin concentration falls below 7.0 g/dL in patients with stable angina and is 8-10 g/dL in those with ACS^[35].

Endoscopic hemostasis of GIB in patients receiving antiplatelet therapy

In patients with GIB, early endoscopy is beneficial for decreasing the length of hospital stay and avoiding surgical intervention^[36,37]. A case-control study reported that there were no serious complications of emergency endoscopy after MI^[17]. During endoscopy, careful removal of clots in an ulcer bed is important to detect the exposed vessel. When active spurting or oozing bleeding or a nonbleeding visible vessel is observed, endoscopic therapy should be provided to patients^[38]. Endoscopic hemostatic options include injection techniques using epinephrine or ethanol, ablative therapies such as use of a heater probe, coagulation with hemostatic forceps or argon plasma coagulation, and mechanical methods such as use of endoclips (Figures 1 and 2). Endoscopic treatment with a combination of epinephrine injection therapy and electrical coagulation or use of endoclips is also effective to achieve better outcomes. Routine second-look endoscopy is not recommended after successful endoscopic hemostasis with intravenous PPI therapy. Transcatheter arterial embolization can be considered for patients in whom endoscopic therapy has failed.

Continuation of antiplatelet therapy

GIB often causes premature cessation of antiplatelet therapy, which increases the thrombotic risk for cardiovascular and cerebrovascular events. A RCT in GIB patients receiving LDA therapy for the secondary prevention of cardiovascular disease showed that interruption of antiplatelet therapy is one of the most important determinants of fatal outcome. Although resumption of LDA therapy after endoscopic hemostasis was associated with a

50% increased risk of recurrent bleeding, the 8-wk mortality rate was significantly lower in the LDA group patients than in the placebo group patients (1.3% vs 12.9%^[39]). Thus, antiplatelet therapy and PPI cotherapy should be resumed immediately after the successful endoscopic control of ulcer bleeding to avoid further ischemic events.

PREVENTION OF GIB IN PATIENTS RECEIVING ANTIPLATELET THERAPY

Optimal duration and dosage of antiplatelet therapy

Risks of GIB increase with the use of multiple antiplatelet or anticoagulant agents and an increase in the duration of medication use. The optimal duration of antiplatelet therapy after PCI is unclear when thrombotic and bleeding risks are both taken into consideration. Although the current guidelines recommend that DAPT should be continued for at least 12 mo in patients receiving DESs during PCI for ACS, the long-term use of DAPT is associated with a higher rate of bleeding events^[40]. These guidelines are based on outcomes using first-generation DESs. Second-generation DESs, such as everolimus-eluting stents and zotarolimus-eluting stents, are now increasingly being used. Compared with first-generation DESs, second-generation DESs have equal or superior antirestenotic effects and lower stent thrombosis rates. Several studies have assessed the safety of a shorter duration of P2Y₁₂ inhibitor administration with second-generation DES use. A retrospective study reported that clopidogrel discontinuation before 1 year of therapy was associated with higher rates of stent thrombosis events for first-generation DESs but not for everolimus-eluting stents^[41]. The Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice trial showed that in patients undergoing PCI with zotarolimus-eluting stent implantation, short-term (3 mo) DAPT was noninferior to long-term (12 mo) DAPT for the occurrence of death, MI, and stroke, without significantly increasing the risk of stent thrombosis^[42]. Accordingly, DAPT duration could be potentially tailored to the type of stent used.

Prasugrel is a third-generation thienopyridine that provides more prompt, potent, and consistent platelet inhibition than does clopidogrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) trial demonstrated that prasugrel use (10 mg/d) resulted in significantly fewer ischemic events^[43]; however, a higher incidence of bleeding was observed with prasugrel use than with clopidogrel use in ACS patients undergoing PCI. Recently, the PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI (PRASFIT-ACS) study in Japanese ACS patients

undergoing PCI showed that a lower dose of prasugrel (3.75 mg/d) was associated with a low incidence of ischemic events, which is similar to the results of the TRITON-TIMI 38 trial, and with a low risk of clinically serious bleeding^[44]. In particular, interethnic differences should be taken into consideration in the management of patients receiving DAPT.

If PCI is required in patients taking oral anticoagulants, DAPT with aspirin and clopidogrel is indicated, but such triple therapy increases the risk of serious bleeding^[27]. Omission of aspirin may be advantageous in such patients. Recently, the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing trial reported that the use of clopidogrel without aspirin was associated with a significant decrease in bleeding complications (2.9% vs 8.8%) without an increase in the rate of thrombotic events^[45]. Therefore, triple therapy may be discouraged in such patients with an indication for oral anticoagulants after PCI.

PPI prophylaxis

In patients receiving antiplatelet therapy, the concomitant use of an antisecretory agent is associated with a reduced risk of upper GIB. In particular, PPI use is associated with a substantial decrease in the risk of upper GIB in both LDA and clopidogrel users^[46]. Moreover, PPIs have been shown to be effective in preventing rebleeding after stabilization of upper GIB, which prevents the premature discontinuation of DAPT^[47]. In patients receiving LDA therapy for the secondary prevention of cardiovascular disease, use of H2RAs was associated with a risk of mucosal erosion but not of ulcer development^[48]. TAK-438, a novel potassium-competitive acid blocker, has also been shown to be as effective as PPIs in the prevention of aspirin-induced ulcer recurrence^[49]. A population-based study from Sweden reported that the risk of gastrointestinal ulcers depended on PPI adherence in patients receiving LDA therapy^[50]. After experiencing GIB, many patients stop receiving LDA therapy, which increases the risk of ischemic events. Therefore, physicians should encourage these patients to continue LDA therapy with PPI prophylaxis.

Potential metabolic interaction between PPIs and clopidogrel

Thienopyridine derivatives are prodrugs, which are metabolized into active forms through complex biochemical reactions involving several cytochrome P450 (CYP) isoforms including CYP2C19, which is also involved in the metabolism of PPIs. Several observational studies in clopidogrel recipients have shown a significant association between PPI use and cardiovascular events^[51,52]. A meta-analysis showed that there was an increased risk (OR =

1.43; 95%CI: 1.15-1.77) of adverse outcomes in patients co-prescribed clopidogrel and a PPI^[53]. Platelet studies have supported the use of PPIs with weaker inhibition of CYP2C19 (e.g., rabeprazole or pantoprazole^[54]). In contrast, in the Clopidogrel and the Optimization of Gastrointestinal Events trial of omeprazole vs placebo in coronary artery disease patients receiving aspirin and clopidogrel, no apparent cardiovascular interaction was observed between clopidogrel and omeprazole^[55]. Taken together, the potential negative interaction between PPI therapy and clopidogrel use is still controversial. Prasugrel is as effective as clopidogrel in the prevention of ischemic events^[43,44,56]. Of note, the platelet inhibitory activity of prasugrel is not affected by CYP2C19. Recently, the DOuble the dose of Clopidogrel or Switch to Prasugrel to Antagonize Proton pump inhibitor Interaction study reported that while the higher platelet inhibitory effect obtained by doubling the clopidogrel dose was completely neutralized by the coadministration of lansoprazole, this drug interaction was not observed with prasugrel^[57]. Furthermore, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes study, which compared prasugrel with clopidogrel in patients with unstable angina or MI without ST-segment elevation^[58], demonstrated that prasugrel was superior to clopidogrel in the subgroup of PPI users. The concomitant use of PPIs with prasugrel or ticagrelor may be beneficial for the prevention of upper GIB in patients receiving DAPT.

CONCLUSION

GIB is a relatively common complication in patients receiving antiplatelet therapy and is associated with an increased risk of recurrent ischemic events and mortality. Prophylaxis with antisecretory drugs such as PPIs reduces the risk of GIB. Early endoscopy is useful for both the diagnosis and the therapeutic management of GIB. Antiplatelet therapy should be resumed immediately after endoscopic hemostasis of GIB, unless the bleeding is life threatening.

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